Eight-year Isotope Summary

Volume 7

SELECTED REFERENCE MATERIAL
UNITED STATES ATOMIC ENERGY PROGRAM

1955

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UNITED STATES OF AMERICA

SELECTED REFERENCE MATERIAL

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VOLUME FOUR Reactor Handbook: Materials
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VOLUME SIX Chemical Processing and Equipment
VOLUME SEVEN Eight-year Isotope Summary
VOLUME EIGHT Information Sources

VOLUME SEVEN

Eight-year Isotope Summary

UNITED STATES OF AMERICA

GENEVA: AUGUST 1955

Foreword

Interchange of scientific and technical knowledge will greatly facilitate the work of the scientists and engineers whose skills will be devoted to the future development of the peaceful uses of atomic energy.

The United States has made available to the world's scientific community a large body of such data. In honor of this historic Conference and to stimulate further exploration and development of the beneficial applications of nuclear energy, the United States Atomic Energy Commission has prepared this special collection of technical data for the use of the delegates and the nations represented.

The purpose of this collection is to provide information concerning the ways that we have found in which fissionable materials can be put to work in nuclear reactors for research purposes and for the production of power and radioisotopes.

It is our sincere hope that this material will be of practical value to the men and women of science and engineering in whose hands the great power of the atom is becoming a benign force for world peace.

Lewis L. Strauss

Chairman, U.S. Atomic Energy Commission

Acknowledgment

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University of California Radiation Laboratory
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Isotopes . . .

AN EIGHT-YEAR SUMMARY OF DISTRIBUTION AND UTILIZATION WITH BIBLIOGRAPHY

UNITED STATES ATOMIC ENERGY COMMISSION

March 1955

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INTRODUCTION

"Isotopes—An Eight-Year Summary of United States Distribution and Utilization" is a résumé of isotope utilization during the first 8½ years of the United States Atomic Energy Commission's distribution program. It is also a supplement to the Three-Year and Five-Year reports of similar title issued by the Commission in 1949 and 1951. This report has been prepared to provide a source for quick reference to the many uses of isotopes and a bibliography on published work with them, categorized by fields of use.

At the cut-off date for the Five-Year Summary (June 30, 1951) the AEC had issued 13,103 authorizations (licenses) to procure isotopes; at the end of 1954, a total of 37,155 authorizations had been issued. During this period the number of United States firms and institutions using radioisotopes has increased from 622 to 2,416. Much of the increased growth has been in industrial utilization; the total number of industrial firms using isotopes increased from 134 to 1,020.

The number of published papers involving the use of isotopes increased from around 3,000 to more than 10,000. More than 7,000 recent open-literature references on work with radioactive and stable isotopes appear in Appendix V. Some special publications of interest to isotope users are listed in Appendix I.

Before the advent of the nuclear reactor, various radioisotopes were made through the use of cyclotrons and other sources of high-speed subatomic particles. They could, however, be produced only in minute quantities, at considerable cost. Although their importance as research tools was immediately recognized, they were available to only a few investigators. The discovery of nuclear fission changed the situation dramatically. The nuclear reactor, in which Uranium 235 is fissioned through a chain reaction process, is a source of radioisotopes in quantities millions of times greater than available previously, with a much greater variety of radiations, and at greatly reduced cost.

Radioisotopes of all the ordinarily stable elements can now be produced. So diversified and extensive have been the methods of artificially transforming atoms that is it now possible to make many more radioactive forms of atoms than the number of stable ones existing in nature. Only 270-odd stable forms, the stable isotopes of 81 of the elements, are known, whereas more than 900 radioactive forms of 100 elements have already been identified, most of which are made artificially.

Radiosiotopes are produced in a nuclear reactor by either of two processes. (1) The two parts into which a uranium atom splits, during the fission process, are radioisotopes of elements from atomic numbers 30 to 64, and can be chemically separated from the remaining uranium. (2) The neutrons, which are emitted when uranium fissions, are present in tremendous numbers and produce radioisotopes from materials inserted into the reactor.

After withdrawal from the reactor, the radioactive objects or materials can often be used directly as sources of radiation. In other cases, radioisotopes can be separated chemically from the irradiated material in concentrated form.

Early in 1946, the Manhattan Engineering District established an Isotopes Branch at Oak Ridge, Tennessee, to institute a distribution program.

The first announcement of radioisotopes available under the distribution program was published in the June 14, 1946 issue of *Science*. The first shipment, a small unit of Carbon 14, was made to the Barnard Free Skin and Cancer Hospital in St. Louis, Mo., on August 2, 1946.

A chronological outline of the development of the isotopes distribution program is given in Appendix II.

Less than 6 months following the start of the distribution program, the Atomic Energy Commission took over the administration of the atomic energy project from the Manhattan Engineering District. In a comparatively short time isotopes distribution became a well-established and growing program.

During the first year of the isotope distribution program, approximately 280 radioisotope shipments were made from Oak Ridge National Laboratory to 83 institutions which used them primarily in fundamental research problems.

At the end of 5 years, approximately 19,300 shipments had gone to over 600 institutions throughout the country, many of whom had begun using the material in applied research and routine applications. More than 2,700 shipments of concentrated stable isotopes had been made. In addition to the domestic distribution, some 1,100 radioisotope shipments had gone to approximately 250 institutions in 31 countries abroad.

During the first 5 years, Oak Ridge National Laboratory made all but a very few of the radioisotope shipments. Today, ORNL remains the primary source of supply but several other AEC Laboratories now distribute radioisotopes. In addition to ORNL, radioisotopes are produced at Argonne National Laboratory, Brookhaven National Laboratory, Mound Laboratory, the National Reactor Testing Station and Hanford Atomic Products Operation.

During 8½ years of distribution, more than 63,990 shipments have gone from ORNL to over 2,400 institutions throughout the country. United States users have received, in addition, more than 3,280 shipments of concentrated stable isotopes. At the close of 1954, 46 countries outside the United States had received 3,173 shipments of radioisotopes and 21 of concentrated stable isotopes at 659 institutions. Distribution of stable isotopes abroad was not begun until July 1954.

In the early days of the radioisotopes program individual shipments averaged about 30 millicuries. At the end of 5 years the average shipment was approximately 130 mc. Today the average shipment is more than 2,360 mc.

The sharp increase in quantity per shipment in part reflects commerial participation in the processing and redistribution of radioisotopes.

The total number of isotope shipments received by ultimate users is several times greater than the quoted number of shipments from ORNL. Many commercial firms purchase radioisotopes in bulk quantities and reprocess them into such forms as labeled compounds, certified pharmaceuticals, and custom-manufactured radiation devices; thus, a single large unit of radioactivity from ORNL may represent hundreds of shipments to individual licensed customers. In addition, thousands of shipments have comprised small license-exempt quantities of radioisotopes. Such license-exempt quantities are readily exchanged between institutions and are not included in the total shipments mentioned above.

More detailed data on growth of the distribution program are contained in Appendix III. Information is furnished on increased isotope shipments and curies shipped per isotope as well as per field of study in which the materials have been used.

Several nuclear reactors are now operating and many more will eventually be built. In reactors tremendous amounts of useful radioisotopes are produced as byproducts. These are truly a great peacetime byproduct—perhaps most important of the atomic age.

Principles of Isotope Utilization

RADIOISOTOPES

Radioisotopes are useful as sources of ionizing radiations and as tracer atoms. As sources of radiation, they are utilized in much the same way as radium and X-rays; as tracers, most of their uses are unique. The fundamental principles involved may be reduced to three major types or modes of use, as shown in Figure 1.

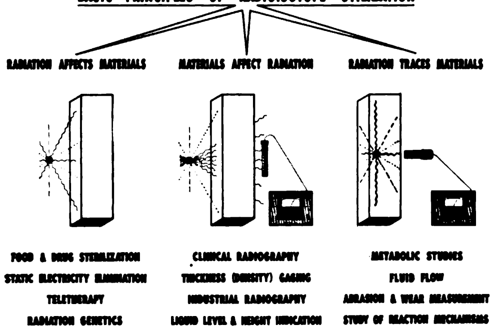


FIGURE 1.

Effect of Radiation on Materials.—In the first mode, the radioisotope is used simply as a fixed source of radiation much as radium and X-ray machines are used. There is a target material which is to be affected in some manner by the radiation. This material may be a cancer patient receiving radiation therapy, a plastic being irradiated to change its properties, or a bag of potatoes being irradiated to prevent decay; it may be the air surrounding a static eliminator or a phosphor incorporating a radioisotope which excites it to luminescence. The ability of radiation to alter a material is important in many ways.

Effect of Materials on Radiation.—In the second mode of use (fig. 1), the effect of the target material on the radiation furnishes information about the material. Here the application is based on measuring the radiation which penetrates or is reflected from the material. The radiation-detection device may be a counter or a photographic emulsion, depending on the application and type of information desired. This is the mode of use in medical radiography when a radioactive source replaces X-ray equipment. In industry it provides an ideal setup for testing purposes and is the basis for most radioisotope applications in product control. Examples of such applications include measuring the thickness of a moving sheet of metal, radiographing the internal structure of a piece of equipment or a casting, and measuring the liquid level in a closed container.

Tracing Atoms Through Their Radioactivity.—In the third mode of use (fig. 1), the radioisotope serves as a tracer to follow the complicated course of individual batches of atoms in physical transfer or chemical or biological reactions. To date this is the most important use of radioisotopes. Radioisotopes are incorporated into the materials of interest, rather than used as fixed sources of radiation physically removed from them. The radiosiotope used in a tracer serves as a tag or label which reveals the presence and identity of the material whether it is involved in a physical or mechanical transfer or in a chemical or biochemical reaction. The material labeled and traced may be water running through a pipe to an underground leak, sugar being utilized in a human being, a raw product for milk production in a cow's body, or an atom transferring from one kind of molecule to another in a chemical reaction.

Radiocompounds*

In many tracer studies isotopes must be incorporated directly into special complex compounds. For example, carbon, one of the major elements in plant and animal systems, is primarily of interest as part of a complex molecule

*The prefix "radio-", denoting radiation, was used by Marie Curie, in 1898, when coining "radioactivity". It has been extended to "radioisotope" and to radioactive elements (radiogold) and substances containing them (radiocompounds, radiocolloid).

such as an amino acid or carbohydrate. Radiocarbon, therefore, is often useful as a tracer only if it is first incorporated into the specific compound to be studied. In many instances it is also necessary to know the exact location of the radioisotope within the molecule, that is, to know which of the atoms within the molecule is labeled. The radioisotope will serve as a true tracer for a compound only as long as it remains part of the molecule. On the other hand, the same tracer atom can often be used to identify a second molecule formed from the first in a chemical sequence.

Isotope-labeled compounds may be prepared either by chemical or biological synthesis. To date nearly 1,000 labeled compounds are known to have been synthesized. Of these more than 500 have been synthesized by chemical means, that is, by procedures similar to those used in preparing the nonradioactive form of the same compound. Some complex labeled compounds which cannot be prepared by ordinary chemical procedures may be synthesized by the biochemical processes of animals and plants. Radioisotopes which have been injected into or fed to an animal may subsequently be extracted from the blood, urine, or tissues as part of complex organic compounds. Isotope-labeled compounds may similarly be extracted from plants.

Several hundred such compounds have been prepared by biological synthesis. The growth of isotope use, especially in the biological fields, will depend to an increasing extent on the availability of a wide variety of labeled compounds.

Detection of Radiation

The useful radiations from radioisotopes are mainly of four types: (1) Alpha particles, identical with the nucleus of a helium atom, are emitted chiefly by isotopes of the heavier elements. They produce intense ionization but have very little penetrating power. (2) Beta particles, identical with negative electrons, have less ionizing power than alpha particles but are much more penetrating. (3) Gamma rays are highly penetrating electromagnetic radiation and do most of their ionizing by means of high-speed electrons they eject from atoms. X-rays are emitted from atoms by a different process but are otherwise identical with gamma rays of the same energy. (4) Positrons are similar to beta particles and have similar ionizing power but are positively charged. They are encountered less frequently than the other types of radiation.

These radiations are detected through their effects on material. Radiation which passes through a material disrupts many of the molecules, producing positively and negatively charged fragments called ions. This ionization is revealed by either the electrical effects or recombination effects of the ions.

The radiations are most commonly detected and counted with sensitive electronic instruments such as geiger counters or scintillation counters. When a particle of radiation enters a geiger counter, it ionizes a gas and thus triggers an electrical discharge. The resulting tiny current is amplified to produce a signal seen, heard, or mechanically counted.

In a scintillation counter, the particle produces a minute flash of light in a liquid or crystal as the disrupted molecules give off energy in recombining. A light-sensitive device converts the flash to a tiny current which is then amplified.

Sensitivity and Specificity of Radioisotopes

Radioisotopes permit materials to be traced in minute quantities—a millionth to a hundred-millionth of the amount detectable by other means. It is easy to detect radiation from isotopes diluted with a billion or 10 billion times as much nonradioactive material. Some isotopes are still detectable after dilutions of more than a trillion.

This means that it would be possible to detect one hundred-millionth of an ounce of radioactive material dispersed, for example, in a 1,000 pound cow.

Even more important than sensitivity is the specificity of radioactive tracer atoms. They can label a specific batch of atoms and enable it to be traced through a series of chemical or physical processes. The labeled atoms can be traced in spite of multiple reactions with numerous other atoms or molecules. This permits the sorting out and untangling of complicated processes which can be followed in no other way. Tracer atoms are, therefore, unequaled

for studying complex chemical or biological processes.

The sensitivity of radioisotope detection, the specificity of the tracer method, and the unique radiation characteristics of individual radioactive species, permit radioisotopes to be used as powerful analytical tools in at least three major ways. These may be referred to as "tracer analysis," "isotope dilution analysis," and "activation analysis."

Radioisotopes as Analytical Tools

Tracer analysis constitutes perhaps the simplest type of tracer application. It is designed to follow the fate of a radioelement or radiomaterial from one stage to another of a reaction or a process. It is primarily useful in determining the distribution of a specified material in a variety of end products. The techniques may be either qualitative or quantitative. They can give information as to "what, when, and how" or can tell "how much." In either case, the advantage is that the determinations can be made at a concentration far below those permitted by other methods. The analysis frequently involves chemical separation of the material at a chosen stage of the process. Measurement is then made of the radioactivity in the different separated fractions.

Isotope dilution analysis is a modification of tracer analysis. It is particularly suited for determining the amount of a substance which is present in a process or system at a concentration too low to be measured by chemical or other methods or which cannot be separated from the other materials for separate measurement. The technique is based on putting into the system a small, known amount of radioactive (labeled) substance similar to the unlabeled substance to be measured.

After a period of mixing, the ratio between labeled and unlabeled substance is the same throughout the system and can be measured with a counter in a sample withdrawn for test purposes. The amount originally in the system can then be computed from its ratio to the known amount added.

An isotope dilution analysis can be likened to a method used by some investigators for estimating the number of fish of a certain kind in a pond. One hundred catfish, for example, can be released into the pond with clipped tails as labels. After sufficient time for thorough mixing of the fish, a sample can be taken with a net. If 100 catfish are removed, 10 of which are marked, it can be assumed that the catfish have been diluted to a ratio of 10 to 90, or 100 labeled to 900 unlabeled. Thus there were 900 catfish already in the pond.

Activation analysis can be used to identify and measure an unknown element in a sample or to determine the concentration of an element known to be in the sample. This is accomplished by exposing the sample to neutrons, as in a nuclear reactor. Some of the atoms of each element present are made radioactive, and those with suitable radiation characteristics can be identified. The technique can either be qualitative or quantitative. It is particularly useful when the concentration of an unknown element is too low to be identified by chemical or spectroscopic methods or where standard methods of analysis are not satisfactory because of interfering contaminants. Examples of applications suited to activation analysis include the determination of minor elements in animal tissue, garden products, and minerals.

STABLE ISOTOPES

Stable isotopes are also valuable as tracers, and their use has led to many important scientific discoveries. Most elements have one or more stable isotopes, which exist in fixed proportions in the element as found in nature. The natural proportions may be changed by increasing the relative abundance of one of the isotopes in a sample of the element. Such a concentrated stable isotope can be followed in a system by taking samples and observing the changes produced in the relative abundance of the isotope as normally found in the system. The isotope's abundance is determined with a mass spectrometer, which sorts out the isotopes of various weights. This method of tracing

atoms is valuable and has found considerable use, but it is not as versatile or as sensitive as the use of radioactive tracers.

Radioactive and stable isotopes have proved especially beneficial in medical and biological research, medical diagnosis, medical therapy, agricultural studies, chemical and physical research, and industrial applications. Their usefulness in each of these broad fields is discussed in the following sections.

Medical and Biological Research

No other field has benefited as profoundly from the ready availability of radioisotopes as the life sciences. As tracer atoms these new tools are so uniquely suitable to solution of problems in this field that they seem almost to have been created for the purpose. Body processes, in sickness and in health, are fundamentally chemical but are carried out on such a dynamic, complex, and microscopic scale that they frequently defy ordinary chemical procedures in their study. Even the sensitive techniques of microchemistry are often too crude and slow to analyze biological processes.

Tracers of various kinds were used in biological studies before the advent of radioisotopes. Dyes can be used in some cases to follow a material and reveal its presence. Peculiar groups of atoms can be joined to molecules of a compound to identify it in later chemical tests Such tracers can follow dynamic processes but have two important defects: (1) they are different from the material they trace so that there is *no* assurance they follow the same chemical pathways and (2) where the traced material is *greatly* diluted during a process, so much of "foreign" tracer must be used that it affects the process itself.

The reason for supremacy of radioactive tracers is thus apparent. They correspond in size and kind to the things they trace. They are not foreign or chemically different. Indeed, they are not *added* to a material—they *are* the material or a true part of it. A molecule of vitamin B–12 is exactly that compound whether it has its cobalt atom in a stable or in a radioactive form, and the body treats it exactly the same. Radioisotopes, therefore, are "natural" tracers and, as far as biological processes are concerned, are no different from other atoms except in their ability to send out signals to identify their presence. These signals are the radiations which can be detected by instruments as previously mentioned.

Except for the important elements oxygen and nitrogen, useful radioactive forms are now available for most elements which enter into biological processes. Sodium, for example, is important in body fluids and tissues and is easily traced by means of its radioisotope, Sodium 24. In one type of application, illustrated in Figure 2, a solution of common salt, or sodium chloride, is labeled with this isotope and injected intravenously. Transfer of sodium to various body sites is then traced and measured by means of the Sodium 24 gamma rays.

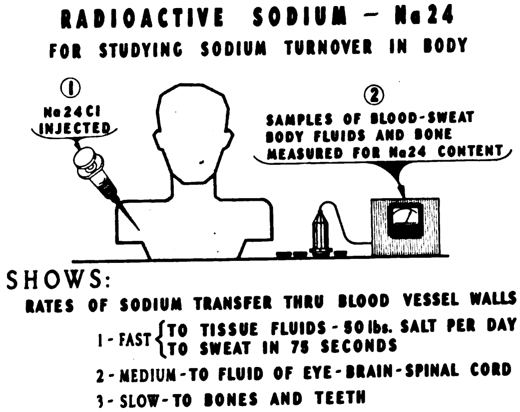


FIGURE 2.

The speed of this transfer and incorporation into body compounds well illustrates the extremely dynamic quality of life processes. Only a few seconds are required for the blood stream to carry the sodium from one arm, through the heart and lungs, and into the other arm. In another type of study, the conversion of injected radiocarbon-labeled acetate into labeled carbon dioxide is found to start almost immediately. The radioactivity in the exhaled breath reaches a peak in about 15 minutes.

Often it is necessary to trace a certain kind of molecule or part of a molecule rather than particular atoms. To meet this need, a growing assortment of hundreds of organic molecules have been provided with radioactive replacements for one or more of their atoms. These tracer compounds, purchased from commercial processers or synthesized by the researcher himself, include such materials as proteins, sugars, amino acids, vitamins, and hormones. With so varied an array of research tools at his

command it is not surprising that the biologist has been able to find answers to many perplexing problems of his science. For many of these problems, radioisotopes provide the first key to a solution.

If the human body were always perfectly healthy, interest in its intricacies would be academic. But, because things go wrong with its structure and processes, it becomes of prime importance to know all that can be learned about it. The body is an exceedingly busy chemical laboratory. It is continuously processing raw material into products suitable for use in building or repairing its parts, or for storage until they will be needed. Food molecules are broken down and their energy is applied to muscle action and other functions. To keep the processes running efficiently, an intricate control system of checks and balances must stay in good working order. This regulatory function is performed primarily by hormones secreted into the blood stream by various glands. Some hormones increase the rate of certain processes and others counteract them if they overcontrol. Still other substances destroy certain hormones if too much is secreted, or stimulate certain glands to overproduce when necessary. Not only rates of reactions but also such things as body temperatures, fluid pressures, and chemical concentrations must be kept within very narrow limits.

In view of this complexity and the many possible changes produced by disease or accident, the need for intense study is immediately apparent. To recognize, understand, and treat abnormal conditions, medical men need to know what is normal, to understand details of processes in the healthy body. Some are so complex that only through radioisotope tracers has any success in unraveling them been achieved.

The cells of the body themselves are the "test tubes" in which most of the chemical processes are carried out. The work of recent years has made this fact clear and much of the research is now being done at the cellular level. Three main subjects are being pursued in this work: (1) the fate of normal metabolites, (2) the action of drugs, and (3) the action of injurious agents.

FATE OF NORMAL METABOLITES

Isotope tracer techniques are being widely employed in studies of the normal chemical activities, or metabolism, of the body. Metabolites, those substances which are essential to these processes or are produced by them, are being labeled and then traced by various techniques.

Calcium Metabolism

Of the 92 natural elements, 15 or 20 are known to be essential to life processes. Most of these have been used in tracer studies designed to show their normal metabolism in the body. For example, radiotracer studies showed that nearly 90 percent of injected calcium concentrated in the bones of young animals; in the old the bone uptake was about 40 percent. Dietary factors have been found which reduce the amount of calcium available to the body. This action may possibly be of value in treating certain diseases. Even more effective is the compound ethylenediaminetetraacetic acid, which has a great affinity for the calcium and tends to remove it from the body.

Protein Metabolism

A large part of the work with metabolites is motivated by the hope of cancer control. If differences can be found between the needs of cancer cells and those of normal tissue it may be possible to retard or prevent the growth of one without seriously affecting the other.

Protein metabolism, because of its fundamental role in life processes, is receiving the greatest share of attention. In a typical study, the essential compound glycine was labeled with Carbon 14 and injected into normal rats and rats with liver tumors. The rats were then sacrificed after various intervals of time so that metabolism was stopped at various stages of completion. The tumors and normal liver tissue in each case were then broken down chemically and the many intermediate compounds, the amino acids which lead to the eventual building of body protein, were separated. The radioactivity of each fraction was measured; any activity demonstrated that the particular

fraction contained parts of the original glycine molecules. From the way in which the C–14 activities varied from one stage of completion to another the experimenters could draw up a "flow scheme" of glycine metabolism. As in almost all such metabolism studies, the same general scheme was found in both normal and cancer tissue although significant differences occurred in the relative importance of some of the steps.

Nucleic Acid Metabolism

Nucleic acid-protein combinations, the nucleoprotein molecules, are the essential material of cell nuclei, including the chromosomes. Nucleic acids, therefore, are fundamental to the life of the cell and to heredity, and the step-by-step processes in their production have received as much attention as those in the case of protein. In general, the same types of tracer techniques are applied to the two; these will be discussed further in relation to anti-metabolite drug action.

Citric Acid Cycle

Tracer techniques have also been used in studies of the citric acid cycle. This cycle, a normal part of cell chemistry, was formerly thought to be missing in malignant cells. However, since C–14-labeled carbon dioxide was found to be given off and citric acid to be produced by such cells when fed C–14-labeled carbohydrates and fatty acids, it was proved to occur in them also.

Hormone Metabolism

Radioactive tagging of various hormones which are known to play an important role in the body has contributed greatly to their understanding. Since a small injected quantity mixes with the same substance produced by the glands, it is possible to find how the body treats its own regulators. In the system of checks and balances, mentioned earlier, the hormones stimulate various chemical processes but, at least in some cases, are continually being destroyed by enzymes which control their amount. Enzymes may, in turn, be controlled in their action by other interfering substances.

The mechanism by which the body controls the insulin hormone is being studied with Iodine 131-labeled insulin. An enzyme-like system in the body, called insulinase, breaks down the insulin molecule. By injecting labeled insulin into mice and then measuring the radioactivity of the breakdown products in their livers, it was found that 1 percent of the insulin is destroyed every 2 minutes during at least the first 2 hours. This destruction must evidently be taken into account in any consideration of diabetes control.

Further study has shown that the liver contains an insulinase inhibitor, an enzyme antagonist, which reduces the destruction by about 78 percent when injected a half-hour before the insulin. Thus, it seems that a balance is normally maintained between the production of insulin and its controlled destruction. If production is low or destruction too rapid, the supply of insulin drops and a diabetic condition develops. The insulinase inhibitor tends to maintain the supply, but whether this substance will be effective as a treatment in diabetes must be determined by clinical trials.

Insulin is necessary in the metabolism of glucose, the form in which most food is absorbed into the blood stream after digestion. Without it the final step of converting sugar to energy or stored fat does not take place. The exact site of the insulin action has not been determined but recent studies with radiocarbon suggest that the hormone helps to transfer glucose through the cell walls and into the cell where it is actually used.

Information is gained in this particular line of research both by labeling insulin and by labeling substances it acts upon. Radioisotopes provide a two-way tool in this respect and permit very effective dual attacks on many similar problems in cause and effect.

A rapid method for measuring pepsin activity in the digestive system would be of benefit to clinical studies of this enzyme in pernicious anemia and cases of gastric ulcer. The breakdown of serum albumin by pepsin, during digestion, produces certain products which can be chemically separated after excretion. After an oral tracer dose of C–14-labeled serum, the

amount of these breakdown products, and thus the pepsin activity, can be determined by counting their C–14 radiation. This method in being developed and may prove of diagnostic value.

Iron Metabolism and Red Cell Life

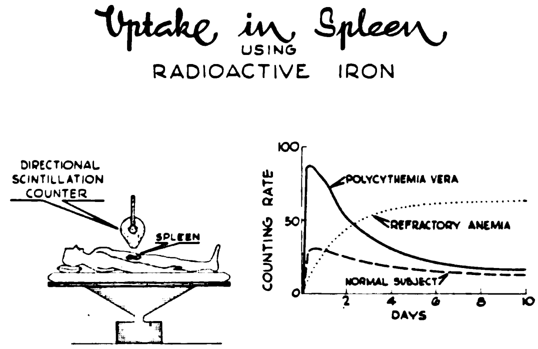
A large and important number of man's diseases are those which affect that most important tissue, the blood. Among these may be mentioned anemia and the cancer-like conditions leukemia and polycythemia vera. The advent of radioactive iron has provided an entirely new and powerful means of studying the production and makeup of blood, both in health and disease, because of the essential role of iron in the blood constituent, hemoglobin. About 65 percent of the body's iron is in the hemoglobin of the red blood cells, 25 percent is stored in special cells of the liver, spleen, and bone marrow, and 10 percent is an essential part of other tissues. Thus, nearly all of an administered dose of radioiron will appear in the blood and blood-forming organs and can be traced over extended periods by means of gamma rays it emits.

Two types of measurements are used. Blood or marrow samples can be taken for detailed analysis, or the activity at a particular site can simply be found with an external counter. The first method is usually used for measuring plasma clearance rate, the rate at which iron carried by the blood plasma from the digestive tract is used up in red cell formation or is stored for future use. The second method gives information on the rate of uptake in a particular organ or tissue.

The iron isotope Fe 59 was used in this way, for example, in a study of red-cell production in persons suffering from polycythemia vera, a disease characterized by over-production of red blood cells. About a tenfold increase in the use of iron was found in such cases, considerably larger than could be accounted for by the increased cell count. In further study, with C–14-labeled glycine, the change of activity in the hemoglobin over a period of time indicated that short-lived cells were being formed in addition to the normal ones of 120-day life. The rapid turnover of these cells seemed to require the large amount of iron which had been a puzzling factor in this disease.

Shortened red-cell life was also found to be the cause of the anemia which so often occurs in cancer cases. Such anemia had usually been attributed to reduced production caused by suppression or replacement of red-cell-forming bone marrow by the malignant growth. However, radioiron tracing showed that red cell production was actually increased in the majority of cases, and that the net loss was due to more rapid death of the cells.

Bone marrow is the primary site of red blood cell production. Tracer studies with radioiron show, however, that in some polycythemia patients the spleen produces an excess of the red cells. By means of a counter directly over the spleen, as indicated in Figure 3, the accumu-



POLYCYTHEMIA VERA—INCREASED RED-CELL PRODUCTION IN SPLEEN
REFRACTORY ANEMIA—SPLEEN DESTROYS RED-CELLS AT ABNORMAL RATE
NORMAL SUBJECT—BALANCE OF PRODUCTION AND DESTRUCTION

FIGURE 3.

lation of iron by the normal spleen is found to rise to a modest volume soon after administration and then to decrease slowly as the iron is metabolized. The uptake in polycythemia, on the other hand, is seen to be abnormally high and rapid because of the greater use of iron in red cell production.

The case of severe refractory anemia is seen in Figure 3 to be quite different in its prolonged uptake and high retention of iron. This reflects the destruction of red blood cells by the spleen, with retention of the breakdown products. Information of this kind can be quite useful inasmuch as removal might be indicated for a spleen which destroys red cells excessively but not for one operating as chief supply of the cells.

Red blood cells are continually being produced and destroyed and knowledge of their

survival time is frequently of great importance. Both radioiron and radiochromium tagging of cells persist throughout the cell lifetime, so that the rate at which redioactivity in the cells decreases with time measures the rate of cell destruction. For example, the technique of blood transfusion has been tremendously improved by development of better storage methods and ways to prepare, ship, and administer whole blood and blood fractions. At the same time, synthetic blood expanders have been developed for emergency replacement of blood plasma. Throughout this work, effectiveness as to preserving the usefulness of the blood for the receiving patient has been evaluated by the survival time of isotope-labeled blood cells.

While a donor's red blood cells survive and perform normally in the recipient's system, the white cells still present a grave problem. Even when transferred directly from the veins of the one to the other, the white cells, as is determined by Phosphorus 32 labeling, are rapidly trapped in the lungs. Indeed, if a large number are transfused, they begin to interfere with lung function. Thereafter they are transferred to the liver but in a fragmented condition. The transfused white cells are thus unable to perform their normal work of resisting disease. This is particularly unfortunate where the recipient's own white cell production has been curtailed, and it is hoped that techniques may soon be developed to permit survival of the cells.

The ability of radioisotopes to trace fluid flow within the body has been valuable in studies of brain circulation. The rate of uptake of a tracer by the brain is a function of the blood flow rate and, with the use of a gamma-emitter, can be determined with an external counter. Various radioisotopes and labeled compounds have been used in this way in determining brain circulation in senile psychoses, cerebral palsy, and epilepsy. Similar studies are leading to better understanding of coma, sleep, anesthesia and, most recently, of pilot blackout during supersonic flight.

Cholesterol Metabolism

A very important part of the contribution by radioisotopes to medical research is being made in studies of cholesterol and its role in arteriosclerosis. This disease has been said to cause more deaths than any other and to be the most important problem in preventive medicine. The loss of elasticity and the thickening of arteries and capillaries which characterize this condition are caused in part, at least, by the deposition of cholesterol in fatty accumulations on their inner surfaces. This substance, sometimes waxy and at other times strikingly crystalline, occurs in every cell of the body and seems to serve as raw material for some of the hormones, bile acids and other essential compounds.

The many tracer studies of cholesterol metabolism are adding bit by bit to our knowledge of this puzzling substance. C–14-labeled acetate fed to rats soon results in the appearance of C–14-cholesterol in many tissues of the body, mostly in the blood and liver. Rates of rise and fall in C–14 activity at the various sites give clues to its production and travels. The rise in activity in blood is found to be later than in liver; this and other considerations show that liver is the site of blood cholesterol production. Rats given a heavy dose of X-rays, before an injection of C–14-acetate, are shown by the tracer to produce cholesterol in the liver at three times the normal rate, a result in accord with other cases of liver damage.

Tracer techniques in such studies are an adjunct to the chemical procedures, of course, rather than a replacement. But as such they give valuable information as to origin of substances whereas chemical tests merely demonstrate their presence. The very high level of cholesterol in the blood of a certain patient with almost complete loss of thyroid function, for example, was naturally thought to be due to an abnormally high production rate. No activity could be found in the blood, however, after a tracer dose of C–14-acetate, showing that cholesterol was in fact not even being produced to a measurable extent. The high level was thus shown to be caused by a defect in cholesterol breakdown and disposal.

Another study with C–14-acetate demonstrated that in the case of cholesterol, as with many other metabolites, the body does not bother to produce a substance if it is supplied

in the diet or otherwise introduced. Dogs fed a high-cholesterol diet showed practically no liver-produced cholesterol in the blood.

If cholesterol in the diet is labeled it can be traced unchanged into the blood. There a portion remains free in the plasma while others are incorporated into red blood cells or are chemically changed in the plasma. When tritium-labeled cholesterol was fed to normal persons and to patients with arteriosclerosis, the tritium activity in the blood fractions was found to be quite different in the two cases. As shown in Figure 4, the concentration of activity in the free cholesterol was normally higher than in other fractions making up the total. In arteriosclerosis it was lower. The hope is that this type of test may lead to the early diagnosis of the disease.

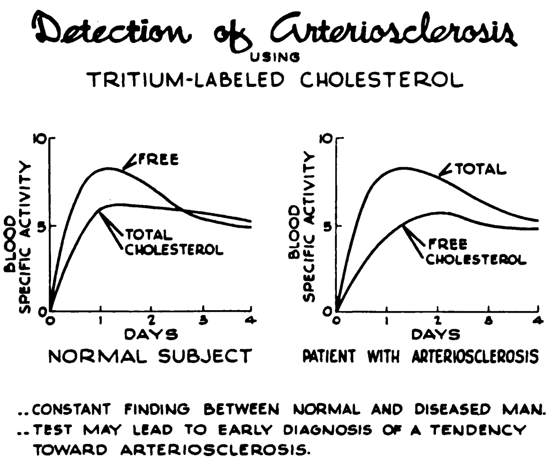


FIGURE 4.

ACTION OF DRUGS

Tracer techniques are also being used in determining the fate and action of materials not considered to be normal metabolites. These include the vast array of medications in common or occasional use, the long list of compounds being tested for possible effectiveness in various diseases, particularly in cancer studies, and substances accidentally introduced into the body.

Anticancer Agents

The intense interest in protein and nucleic acid metabolism, as mentioned before, stems in part from the possibility of exploiting differences between cancer and normal cells. If withholding a substance were found to be more harmful to the "well-being" of malignant tissue than of normal tissue, the former could possibly be starved. Or if the blocking of a step in the metabolic process were especially harmful to the cancer cells, a similar result should be obtained. A third possibility is seen in case a particular material is used to a greater extent by cancer cells; supplying the material in radioactive form would cause the cells to be irradiated from within and might lead to their destruction.

Of these three possibilities, the first has not yet been realized and the third, despite many trials with different radioisotopes and radiocompounds, has proved to be effective only in the case of Iodine 131 in some thyroid cancer. The remaining possibility, drug therapy or the chemotherapeutic approach, has received a great amount of attention in recent years. While most of the work has been done with experimental animals, it has been possible to extend the experiments to clinical trials with certain drugs.

The building process is considerably faster in malignant than in normal cells and so an impairment of nucleic acid synthesis can result in greater harm to cancer and to leukemic blood cells than to healthy tissue. Many of the chemical reactions in metabolism are made to proceed by enzymes. Hope, therefore, lies in the fact that a step from one intermediate product to another can be blocked by interfering with the particular enzyme. The drug amethopterin has received most attention in this respect because of its anti-enzymatic action and its resulting therapeutic effect in certain leukemias. This type of action is indicated in Figure 5. The drug seems to block the conversion of folic acid to an enzyme which is essential in the step from certain intermediate building blocks to forerunners (precursors) of nucleic acid.

A basis is thus established for chemotherapy of cancer. Radioisotope-labeled metabolites have been widely used in determining metabolic effects in extended trials of other possible anticancer drugs. It has been found that simultaneous use of two drugs can be particularly effective if they block enzymes at different

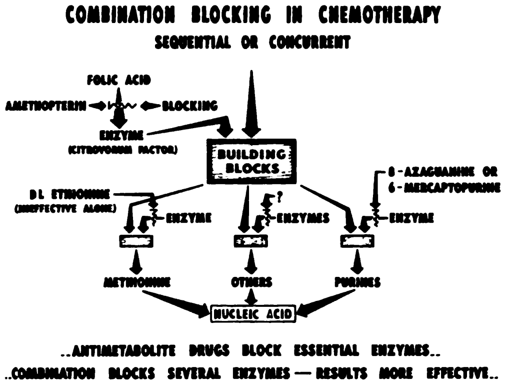


FIGURE 5.

points in the same metabolic pathway, as indicated in the figure. Concurrent use of two or more drugs can also overcome a drug resistance, acquired against any one of them, by blocking other necessary pathways.

It has been found that separated white blood cells, the leukocytes, can be used outside the body as an experimental medium in tracer studies of protein and nucleic acid metabolism. Differences in metabolism occur, depending on the origin of the cells, and amethopterin is found to have its usual inhibitory effect. A study is being made in which this and other drugs used clinically, especially in leukemia, will be tested on the leukocytes. If it should develop that a leukemic person's white cells in a test tube react metabolically to drugs in the same way and to the same extent as the person himself, a clinical method may evolve for selecting the best drug for treating a given patient.

The search for effective anti-cancer agents is made more difficult by the diversity among cancers themselves. Differences between types are frequently more pronounced than between some of them and normal tissues. Tracer methods are helping to bring order to this complex problem. In a typical study, mice bearing different types of malignancies were injected with various drugs known or suspected to have an effect on tumor metabolism. Labeled metabolites, known from other tracer work to be involved in the metabolic chains of reactions leading to protein, were then administered. The distribution of radioactivity later found in separated metabolites from the tumors then showed the relative blocking effect of the drugs on the different reactions and best drugs for the different tumors.

Among the host of drugs, other than anti-cancer agents, which have been isotopically labeled and traced in action, may be mentioned antibiotics such as penicillin, the sulfa drugs, alkaloids such as digitalis and morphine, sugar substitutes, and hypnotics such as pentothal and the barbiturates.

ACTION OF INJURIOUS AGENTS

Tracer techniques with radiosotopes permit detailed study of the effects of many agents causing actual bodily harm. Harmful substances or organisms can be labeled and then traced in experimental animals or in man himself. In addition, tracer methods can be applied to studies of the processes which are interfered with in the body.

Carcinogens

Many investigations have been made on substances known or suspected to cause cancer. Certain organic and inorganic compounds have long been known to induce cancer formation. In fact, some have been used experimentally to produce tumors in animal studies and to study cancer genesis and metabolism in general.

An outstanding class of these compounds is composed of various hydrocarbons, certain coal-tar products in particular. In a typical tracer study of these compounds, C–14-labeled dibenzanthracene was applied to the skin of mice. After a short time, the compound or one of its products, as identified by its radioactivity, was found chemically bound to protein in the skin cells. Other hydrocarbons known to produce cancer have similarly been found to unite with cell protein in various tissues of the body and this action is thus thought to be important to their effect.

One carcinogen in particular, 2-acetylaminofluorene, gives rise to cancers of different cellular types and in a variety of tissues remote from its point of entrance into the body. The ability of chemists to label selected parts of a molecule is being applied to this compound so

that each part in turn can be traced. As it is broken down in the body, the parts are traced to determine their individual distribution. It is hoped that a correspondence between the pattern of cancer distribution and that of the compound or one of its products may show which substance is the actual cause of the growths.

Radiation Damage

Radiation damage is a comparatively new hazard to man's well-being, starting with his first use of X-rays and radioactivity at about the turn of the century. A gamma or X-ray or a high-speed nuclear particle disrupts the molecules in its path. Chemical substances are produced which destroy the normal metabolic processes within the cells and may lead to their death. Studies of this action are important not only in devising ways to combat or forestall radiation damage but also in using and controlling it in medical therapy. Practically all the tracer studies conducted in other lines of medical research have been repeated in investigating the metabolic changes induced by radiation.

Some of the molecular fragments produced by radiation prevent normal cell processes by oxidizing and thus altering the components. Damage is greatly reduced by the addition of substances, such as cysteamine, which strongly compete for oxygen. Administered to a patient about to be given a therapeutic dose of X-rays, for example, such medication may greatly reduce the general damage to the system which might otherwise result.

Other Injurious Agents

The tracer technique has been applied in studies of a great many other damaging agents. The most important members of this category are, of course, the germs and viruses. These have been labeled and traced within the body to determine their distribution in relation to the onset of disease processes. Tracer studies of the processes they alter, the other side of the dual approach mentioned before, have increased our understanding of some diseases and aided in planning for their control.

Allergies have been investigated through the use of radioisotopes. In the case of ordinary ragweed pollen, for example, the injurious agent was tagged by growing the ragweed plant in an atmosphere of C–14-labeled carbon dioxide so that the entire plant, including the pollen, became radioactive. Differences could then be traced in the pollen's action in sensitive and nonsensitive patients.

The profound changes induced by toxicants and poisons have been traced in metabolic studies and, where the agent itself is labeled and traced, the extreme sensitivity of the technique allows positive results with minute, unharmful amounts of the material.

MISCELLANEOUS STUDIES

The lines of research which have been individually mentioned are, of course, only a representative few of the vast number under way. Practically every phase of human physiology and pathology has derived benefits from the radioisotope techniques in research. Brief mention may be made of a few other areas of study.

Since most of the body consists of fluids of various sorts, much of the research on normal and disturbed body functions relates to fluid volumes, flow, and transfer through cell and tissue walls. The availability of radioactive tracers is particularly fortunate for this type of study. The volume of a fluid can be found by the isotope dilution technique as previously described. Flow is easily measured by timing the arrival of a bit of tracer material at different points of a system, and drainage from tissues by noting a decreasing radioactivity at the area of interest.

Most of the body chemistry is dependent on membrane permeability to certain substances. For example, substances unwanted in particular reactions, as in a cell, are refused entrance while others can enter only at rates best suiting the reaction process. The ability of a substance to pass through a membrane, and the rate of passage, can be found by adding a radioactive tracer at one side and noting the arrival of activity in the otherwise exactly similar substance on the other side. Frequently radio-

active tracers furnish the only method for making such determinations.

Figure 6 is indicative of this type of study, and illustrates the nicety to which potassium and sodium ions, in and around a nerve cell, are normally kept at their respective relative concentrations. Recent studies show that these ions, as they enter and leave, produce the minute electrical impulses associated with the functioning of the nervous system. The quantities involved are so small, a few billionths of a gram of ions per impulse, that only the radioactive tracer technique could have determined them.

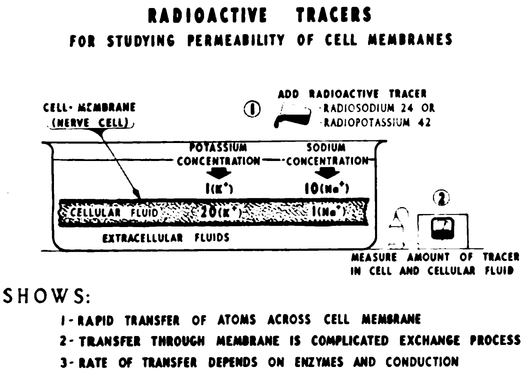


FIGURE 6.

Radioactive potassium has also been used to demonstrate that the potassium ion is related to muscle function. Muscle cells affected by muscular dystrophy, for example, have been found unable to retain the normal amount of the ions.

In tracer studies of permeability to pure water, only the oxygen atom or one or both of the hydrogen atoms can be used as a label for the H_2O molecule. No convenient oxygen isotope is available but the isotopes of hydrogen—stable deuterium and radioactive tritium—have been used for this purpose. A study has been made of the rate at which water normally enters the blood stream from different parts of the digestive system, using deuterium as a tracer. Measurements of the changing deuterium concentration in the blood showed that 95 percent of water in the stomach enters the blood in 54 minutes, while absorption from the small bowel amounts to 95 percent in only 10 minutes.

Radioactive tracing has frequently been ranked with the microscope in importance to biology and medicine. It is therefore to be expected that the two, in combination, would provide a particularly powerful research tool. In tissue autoradiography, illustrated by Figure 7, the distribution of a radioactive substance

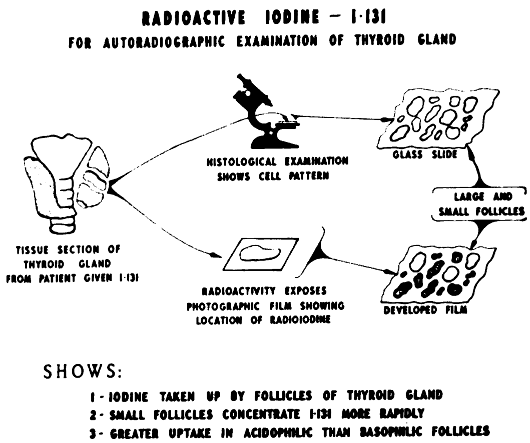


FIGURE 7.

among the cells, and even among the parts of a single cell, can be seen. In a typical application of this technique, a photographic emulsion is placed against a section of tissue which has been surgically removed from the body, after a labeled material has had time to attain its characteristic distribution. The emulsion becomes exposed by the radiation wherever the radioisotope occurs. By examining with a microscope the developed emulsion and the cells themselves, or by comparison of enlarged photographs of the two, the investigator can relate the traced material to particular cell structures.

Color may perhaps be added to autoradiography through an extension of this technique under development. The new concept involves the differential absorption of the radiations from different isotopes by color film. It is hoped that this will allow simultaneous tracing of two or more tagged substances. Radiations of different types and energies have been found to penetrate and expose the layers of three-layer color film to different extents, and thus to produce differently colored images. Carbon 14, Calcium 45, Sulfur 35, Phosphorus 32, and

Iodine 131 were found to give characteristic colors ranging from red-blue through yellow to white.

ANIMAL AND PLANT STUDIES IN MEDICINE

Medical research gains much benefit from animal and plant studies and in many ways is directly dependent upon them. Life processes are quite similar wherever found, chiefly because of the universal occurrence of the cell as a fundamental building block which can grow by division into others of its kind. Radioactive tracers have found widespread use in these parallel sciences, and many of the results obtained have been of profound importance to medicine.

As our understanding of metabolic processes continues to grow, through modern research methods, the closeness of this parallel becomes even more apparent. As an example, the present need to synthesize a better artificial rubber molecule has renewed the interest in Nature's successes along this line. From tracer studies of the plant chemistry involved in the building of the molecule from labeled acetate, a close correspondence has been found between rubber synthesis in plants and cholesterol synthesis in man.

The studies of concern to agriculture and animal husbandry are discussed in the section on agricultural studies below. Of chief interest here are those investigations involving life, at its various lower levels, which have medical

The ultimate experimental animal is, of course, man himself and, after judicious trials on human subjects, a great portion of the research has left the laboratory to become a part of clinical diagnosis and therapy.

strains of rats and mice provide the statistics where mammalian tissues and systems are required, and cats, dogs, and monkeys where organs and general physiology even closer to the human are of interest. Finally, where a system comparable in sheer size to man himself is needed, burros are given radiation doses or other treatment under study.

small animals or microorganisms; (3) genetically pure strains, unobtainable in man, are usually needed to avoid unknown heredity factors; and (4) much smaller amounts of a possibly very expensive tracer preparation need be used in smaller biological systems.

The fundamental processes in cell metabolism occur in microorganisms as well as in man, and much of the tracer work in determining the precursor-product schemes is done, for example, with bacterial and yeast cultures. Laboratory implications. Man is not expendable and, for a number of reasons, lower animals are usually used to take his place, at least in the early stages of an experiment. Four of the reasons may be mentioned: (1) effects may be harmful; (2) need for statistical accuracy calls for repeated trials, and sometimes generations, in tens and even thousands of cases, thus dictating the use of

Medical Diagnosis

In medical diagnosis, as in research, radioisotopes furnish a powerful means for gaining knowledge of body processes. Hundreds of hospitals consider them as part of their regular equipment. Some techniques are now routine diagnostic procedures. On the other hand, much of the diagnostic work still borders on the experimental. The widespread application of radioisotopes to medicine is only a few years old and is still a rich field for development.

The many diagnostic uses of radioisotopes can be grouped in four categories: (1) dilution techniques, (2) flow or diffusion measurements, (3) biochemical concentration, and (4) radiography.

DILUTION TECHNIQUES

Blood Volume

Many diagnostic applications are based on measurement of volume or amount of a substance in the body by means of the isotope dilution technique. It frequently becomes necessary to determine a patient's blood volume, for example, before surgery or administration of a blood additive. Many radioisotopes and variations of techniques have been used for this purpose. In a typical application, I–131-labeled human serum albumin is injected into the blood stream. After sufficient time for mixing (10 to 15 minutes), a sample of blood is withdrawn and measured for radioactivity. The degree to which the label has become diluted then gives a measure of the blood volume.

The mass or amount of the red blood cells themselves is determined by either of two methods. In the first, where radioiron is employed to label the cells, labeling must be done within and by the body. Since the dilution technique requires that the patient's blood be kept free of any radioactivity except that in the tracer material, this method involves the use of a second person, in whom the labeling can be done. The radioisotope is introduced into his blood stream, and after a sufficient time for the iron to become incorporated into the hemoglobin of the cells, a volume of blood is withdrawn. Labeled red blood cells are separated from plasma and injected into the patient for the dilution study.

The second method involves labeling cells with radiochromium, Cr–51. Since this can be done outside the body, a donor is not needed. The radioisotope, as sodium chromate, is mixed with a sample of the patient's blood. After about an hour, the red cells are separated in a centrifuge and, after washing, are reinjected into the patient for the dilution study. This method is comparatively simple and is coming into routine use.

Simultaneous measurements of blood plasma volume and red cell mass have been made using Cr–51 in the form of chromate and chromium chloride. Since the first penetrates cells while the second becomes fixed in plasma, the two measurements can be kept separate.

It is interesting to note that United Nations troops were tested with radioactive tracers for loss of blood, before transfusions on the battle field in Korea, and that many of them doubtlessly owe their lives to the increased accuracy of these newer techniques.

Water Volume

In many abnormal conditions, such as edema, it becomes important to know the volume of total body water and of water in intracellular and extracellular spaces. Here, again, dilution techniques provide the answer, the choice of labeling material determining the type of results obtained. Total water is measured from the dilution of deuterium- or tritium-labeled water. The mixing of a tracer amount

throughout the body and in the cells is essentially complete in about an hour, and a dilution sample can be taken at that time. No convenient method exists for measuring volume within the cells, but this can be found as the difference between total body water and extracellular water. The latter is measured by means of a tracer which penetrates blood vessel walls but cannot enter cells, or can enter only slowly. Certain substances with large molecules, such as inulin and sucrose, have been used for the purpose but faster mixing in the extracellular fluid is obtained with radioactive tracers such as Sodium 24 and Bromine 82. These slowly enter the cells and so only a short period of mixing is allowed before the measurement is made.

FLOW OR DIFFUSION MEASUREMENTS

Because of the dynamic qualities of body processes, many diagnoses are concerned with flow or diffusion of substances. Changes in counting rate at a certain place, due to movements and changing concentrations of a radioactive tracer, provide the necessary data.

Cardiac Output

Knowledge of the heart's output is invaluable in diagnosis of many heart disorders. As with other pumps, the efficiency of the heart can be judged by the flow it induces, measured in liters per minute or similar units. To measure this output, a small amount of I–131-labeled human serum albumin is injected into an arm vein. The resulting peak of activity in the blood is measured after it is pumped through the heart and then passes a certain point in an artery. The peak, recorded automatically as a curve on a strip chart, is somewhat spread out by this time and the flow rate is calculated from its area and duration.

Peripheral Vascular Disorders

Radioactive tracers have long been used to measure the blood supply to extremities and to measure the rate at which needed substances are passed to the tissues. If a saline solution labeled with radiosodium, for example, is injected into an arm vein and the foot is placed against a counter, the recorded activity begins to rise as sodium reaches the foot and pervades the tissues. In a normal subject the activity rises evenly and begins to level off within 30 to 40 minutes. The increase is the result of interchange of labeled sodium between blood and extracellular fluids. Equilibrium is established when the number of sodium atoms leaving the blood vessels is equal to the number returning to the circulation from fluids of the foot. In most patients with a peripheral vascular disorder the equilibrium value is lower and is reached more gradually, demonstrating an impairment in this supply system.

A similar technique is used in cases where the head of the femur has broken off. This ball of the ball-and-socket joint at the hip is attached to the thigh bone by a thin neck which is easily broken, especially in older people. If a break occurs, the surgeon must decide whether to graft the ball back on or to replace it with a pinned metal ball. The decision frequently rests on the question of an adequate blood supply to the ball, through the network of blood vessels still attached. After a tracer dose of Phosphorus 32 is put in the blood stream, a comparison is made with a directional counter of the activity above and below the break.

A somewhat different technique is shown in Figure 8, where a suspected constriction of blood vessels is found, after a tracer injection, by comparing the patterns of blood flow simul-

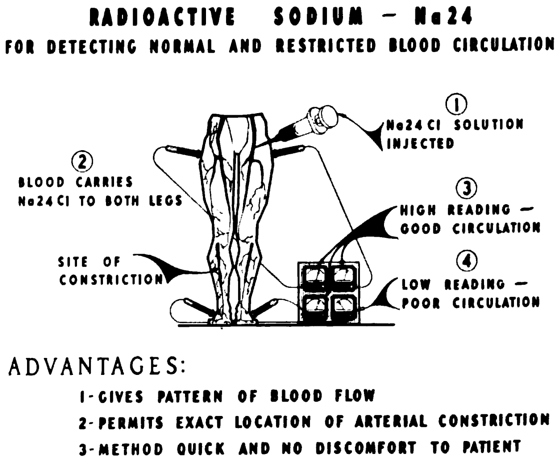


FIGURE 8.

taneously in the two legs. The method is also valuable for measuring the improvement in vascular function as a result of therapeutic procedures. It can also help in deciding upon the site of amputation if surgery becomes necessary.

The ability to trace blood circulation and accumulation at particular sites has been valuable also in cases of hemorrhage, burns, and fistulae between organs as in stab wounds. A reverse procedure is frequently used in determining blood circulation at a particular site by the rate at which it can remove an injected substance. Here a tracer material such as Sodium 24 chloride is injected into the tissues and the manner in which the activity decreases, as measured with a counter over the site, gives a measure of the clearance rate. This technique has been valuable to the plastic surgeon in the case of pedicle grafts. By watching the rate at which the tracer leaves the grafted tissue, he can tell whether circulation has been achieved, rather than waiting to find whether the graft "takes" or sloughs off.

BIOCHEMICAL PLACEMENT

Many diagnostic uses of radioisotopes involve selective accumulation of a tracer dose in certain tissues, where it can be found with a counter. The material is introduced into the body either orally or by injection and then, by physiological processes, is concentrated more at some sites than at others.

Two types of determinations can be made by this method. First, particular tissues, such as tumors, can be located if they are known to accumulate a certain element or compound. Second, the condition of a tissue can be determined from the rate at which the accumulation occurs.

More of the material may appear at one place than at others merely because a certain tissue absorbs it faster than others. This type of accumulation can only be used, therefore, until the other tissues "catch up" and the distribution becomes general. On the other hand, a certain tissue may have a special affinity for a material. In other instances, it may first be distributed fairly uniformly throughout the body but then be released at a slower rate by a certain tissue than by others.

The time at which the selective or differential concentration of a tracer is most useful may be a few minutes or even hours or days after the tracer is introduced. The degree of concentration also varies in different cases, being highly selective in some and low in others.

Thyroid Disorders

The best known and most widely used example of selective absorption is the accumulation of iodine by the thryoid gland. Other tissues and organs of the body have very little use for this element while the thyroid employs large amounts of it in manufacturing the thyroid hormone, thyroxin. The thyroid gland picks up and utilizes nearly all of the iodine retained in the human system, normally about 1,000 times as much as surrounding tissue. This selective action provides practically ideal conditions for radioiodine tracer studies of the gland and its functions.

The rate of iodine pickup is above normal in hyperthyroidism (overactivity of the thyroid) and below normal in hypothyroidism (underactivity). Diagnosticians, with radiation counting instruments, can easily determine this rate in any individual after administration of a small tracer dose. The diagnostic method now in use by hundreds of hospitals and private practitioners involves simply the placement of a counter over the patient's throat to measure the accumulation of radioactivity in the thyroid after a drink of weak radioiodine solution. In many places the technique is used routinely on all thyroid cases and has been made even easier by the availability of gelatin capsules which contain a correct tracer amount of the material for the patient to swallow. The rate and degree of radioiodine accumulation in the urine and in various blood fractions are also important in determining the thyroid health picture.

Delineation of Organs

The actual size and shape of an organ frequently need to be known, as in diagnosing a pathological condition, planning for surgery, or

determining organ bulk in order to plan a proper size of therapeutic dose. In the case of the thyroid gland this is done with a highly directional counter which "sees" only a very small area and thus can pinpoint the source which is producing the counts. After a tracer dose of radioiodine, such a counter can be moved about over the patient's neck to find the pattern of activity and thus to outline the thyroid tissue itself.

A refinement of this scanning method which has come into favor uses a motor-driven carriage to move the counter back and forth, and stepwise, over the throat. Amplified pulses from the counter actuate a marking pen which is moved back and forth continuously over a chart at the same rate as the counter. The resulting pen marks indicate the locations of the radioactivity and, as the counter and pen move down line by line, an actual picture of the thyroid gland is built up. Quite detailed pictures are obtained in this way, with nonfunctioning and over-functioning areas of the gland clearly distinguished. Successful use of this scanning method in the case of the thyroid gland has led to its use with other organs.

Location and Extent of Malignancy

Cancers are known to inherit some of the characteristics of their parent tissues. Those of the thyroid gland, for example, are sometimes able to accumulate iodine and even to manufacture the hormone. This uncertain concentration, however, is of very little or no use in locating cancer in the gland itself because of the high concentration in the surrounding gland tissue.

Where the thyroid cancer has metastasized, or spread, to other parts of the body, as it

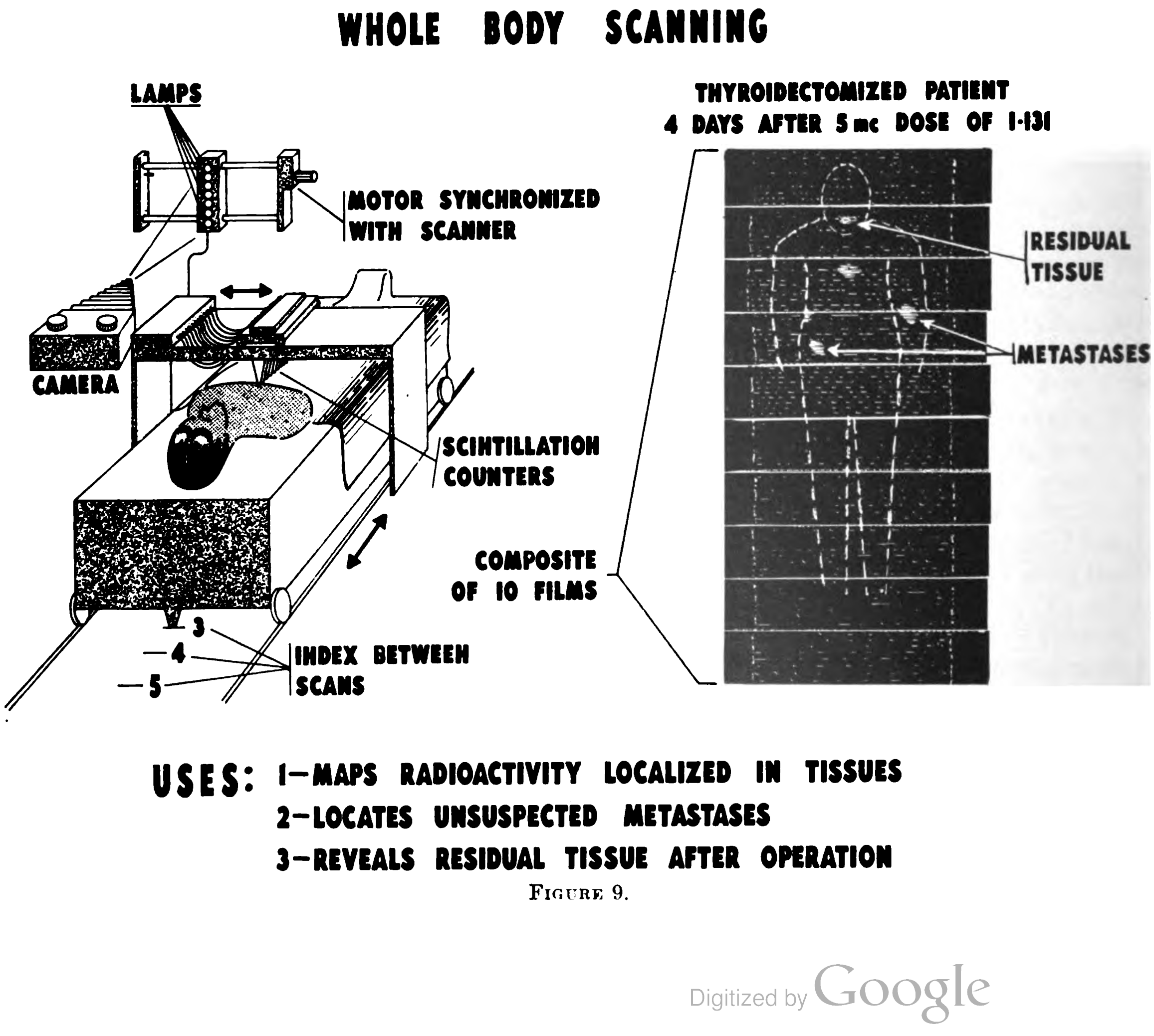


FIGURE 9.

usually does, the offshoots may continue to grow with thyroid characteristics. These thyroid metastases vary greatly in their ability to accumulate iodine. This uncertainty in iodine pickup is unfortunate in so far as finding the offshoots is concerned. Nevertheless, a large enough proportion of them show activity to make radioactive tracing a valuable diagnostic procedure. Many such cancerous lesions have been found which would not have been located by other available means.

The overpowering affinity of the normal thyroid tissue for iodine prevents any appreciable accumulation by the cancer cells. When the thyroid gland is removed by surgery or otherwise inactivated, the cancer offshoots receive more thyroid-stimulating hormone from the pituitary gland. Those which are able to take up iodine then increase their uptake and can more easily be found and treated.

Figure 9 illustrates a refinement of the automatic scanner which permits a survey of the entire body. This type of instrument has frequently demonstrated the presence of metastatic cancers which were otherwise unsuspected.

Tracer methods are assisting in the location of brain tumors in a number of hospitals.

The comparatively weak beta radiation from P–32 will not penetrate the brain and skull well enough to allow detection of tumors except by internal probe ,whereas the gamma radiation of I–131 has been found useful for locating tumors through the intact skull. This use is illustrated in Figure 10. Brain tissue is normally protected by the so-called blood-brain barrier which

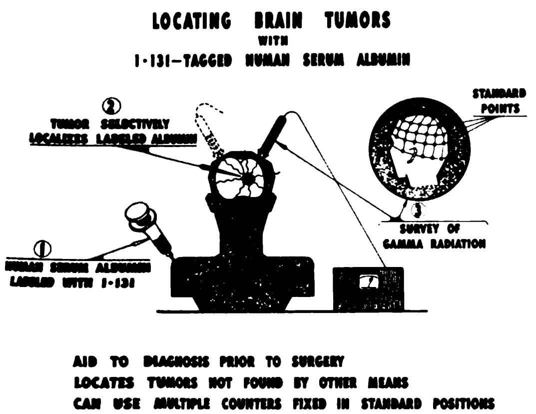


FIGURE 10.

prevents the transfer of many substances from the blood stream which otherwise would be absorbed. This barrier is impaired in lesions, and substances may temporarily accumulate in the extracellular spaces and cells of a tumor while being excluded from surrounding tissue. Various substances have been tagged with I–131 for concentration in brain tumors by this action. A survey over the skull with a directional counter may then help to indicate the position of the growth. Diiodofluorescein has been much used as a carrier of I–131 for this purpose but has been largely supplanted by iodinated human serum albumin.

Accurate outlining of radioactive areas is considerably more difficult in the brain than in the thyroid. Because of the increased amount of surrounding structure a considerable degree of gamma-ray scattering occurs which blurs the outlines. Also, concentrations of radioactivity ranging only from 1.6 to 29 relative to surrounding brain tissue have been reported, whereas a relative concentration of several thousand is characteristic of the thyroid. When so little variation exists between tumor and surrounding tissue, scattered radiation and background radiation from natural sources interfere seriously with the diagnosis.

These difficulties have been avoided by the use of a highly directional scintillation counter, with a recording system which accepts only those pulses from the counter which correspond in energy to the primary gamma ray of I–131. Only I–131 concentrations are depicted on the resulting gammagraph because scattered radiation is too degraded in energy from the primary value. Background radiation is either too high or too low in energy to be accepted.

Another scanning device for brain tumors takes advantage of a peculiar property of positrons. The decay of a positron, immediately after its emission by a radioisotope, is attended by the production of two gamma rays which travel in opposite directions. The device employs two opposed scintillation counters, one on each side of the patient's head. It is designed to count only gamma ray coincidences, counts which occur simultaneously in both counters. Therefore, it can detect positron disintegrations without also counting scattered and background radiation. The device is used

to detect positron-emitting substances, such as Copper 64 and Arsenic 74, concentrated by the tumors.

Benign vs. Malignant Lesions

Because of the rapid turnover of phosphorus in areas of accelerated metabolism, there is a temporary 8- to 100-fold concentration of P–32 in such areas after a diagnostic dose. Where this concentration occurs near a surface accessible to a counter, as in the breast, testes, or the eye, the fraction of the dose taken up by the cancer can be determined by a sensitive radiation counter. The growth or shrinking of the lesion under therapy may thus be determined by periodic checks. Since some benign tumors and other rapidly growing tissue also concentrate the isotope, malignancy cannot definitely be distinguished. Some clinicians, however, find the method useful even in original diagnosis for cancer.

The beta particles from P–32 cannot penetrate to a counter through more than 7 or 8 millimeters of tissue. Radiopotassium (K–42) has been used to extend the method to cancer at greater depths. Potassium, too, has a rapid turnover in growing tissue, while its radioisotope emits a 1.5-Mev gamma ray which is easily detected by a scintillation counter.

RADIOGRAPHY

The taking of "X-ray pictures," with beams from X-ray tubes, has been an important part of diagnosis since the turn of the century. Devices which utilize X-ray emitting radioisotopes as sources have now been developed for certain diagnostic purposes. These portable units have particular value in isolated locations where conventional, bulky X-ray equipment is not practical.

Such a portable X-ray unit using radiothulium (Tm–170), has been developed in a very simple form. A cylindrical piece of lead which can be grasped in the hand has a curved passageway through the center along which a small thulium source can be slid by means of a photographic shutter-release cable. When not in use the source is located at the center in shielded position; in use, it is moved to an open port at the end by means of the cable. Such a source, 15 to 30 inches away from an object, can produce an acceptable radiograph in a few seconds. The resulting picture is not as sharply detailed as those obtained with conventional X-ray equipment but is satisfactory for many purposes of diagnosis.

A somewhat similar device has been developed using the radioisotope Strontium 90. In the thulium unit described above, the X-rays are emitted by an ytterbium isotope formed in the decay of Tm–170. Strontium 90, on the other hand, decays to an isotope which emits beta rays. The beta particles, or electrons, in leaving the atoms and traversing the material in the source and holder, generate X-rays just as the electron beam does when it hits the target in an X-ray tube.

An especially useful combination is provided by one of these Tm–170 or Sr–90 X-ray sources and a film holder incorporating a self-contained development system. In this, a capsule contains film-developing chemicals which can be released and spread over the film without removing it from the holder. A finished picture is produced in about 1 minute. Such a combination can be extremely valuable in an army field hospital, for example, where neither X-ray equipment nor dark room is available.

Recent expansion and improvement in the diagnostic use of radioisotopes are due, in large measure, to advances in instrumentation. Development of the scintillation counter and of counting circuits which discriminate between radioisotope radiations, and between these and background radiation, have greatly increased the sensitivity of detection. More definitive results and greater accuracy can now be obtained. Moreover, increased sensitivity permits the use of less radioactivity. Tracer amounts of radioisotopes need result in radiation doses no larger than those received during X-ray diagnosis.

Hundreds of thousands of patients have been diagnosed with radioisotopes in the United States. Iodine 131 tests, alone, have been used over a quarter-million times. These numbers are increasing rapidly as more physicians receive training in clinical use of radioisotopes, and as techniques and instrumentation continue to improve.

Medical Therapy

The possibility of using radioactivity in medical therapy was recognized shortly after the discovery of radium in 1898. Since early in the present century, radium has been used in teletherapy, or treatment at a distance, in which it provides an external beam of radiation to destroy or retard tissue growth. It has also found widespread use in the form of surface applicators and insertions in tissues for local irradiation.

With the discovery of artificial radioactivity the possibility of a third mode of treatment was recognized. This was the possibility that radioactive forms of those elements which take part in body processes could be introduced into the body, and that the body would concentrate them in certain tissues for localized irradiation. Early hopes regarding this technique have not all been realized, since the radioisotope frequently is not concentrated to a sufficient degree to allow its destruction of the diseased tissue without damage to healthy tissues. Biochemical placement of therapeutic amounts of lethal radiation, therefore, can be relied upon only in certain types of cases. In these, however, valuable results are obtained. More positive action can be obtained in other instances by various techniques developed for inserting or injecting the radioisotopes directly into tissues.

The therapeutic uses of radioisotopes are grouped here under the three modes of application mentioned above: (1) biochemical placement of radioisotopes, (2) physical placement, and (3) teletherapy.

BIOCHEMICAL PLACEMENT

Two chief types of mechanism account for biochemical concentration of materials in certain tissues. The first is the *selective absorption* of a material needed by a particular tissue for its special function, while the second is *differential turnover* due to the increased use of a material in the more rapid metabolism of a particular tissue.

Selective Absorption

The best known and almost classic example of a special affinity between a tissue and a particular substance is that of the thyroid gland and iodine. The use of this selective action to introduce a sufficiently destructive amount of radioiodine to the gland, as illustrated in Figure 11, is now considered a highly practical form of therapy for hyperthyroidism (including thyrotoxicosis, Graves's disease, etc.) It is especially useful where surgery would be too dangerous or thyroid drugs cannot be given or are unsuitable. This treatment has largely supplanted surgical removal in a great many hospitals. Over 400 institutions are using I–131 for this purpose and tens of thousands of patients have been treated. It has been estimated that 90 percent of the hyperthyroid cases treated with I–131 are brought under control in 2 to 4 months.

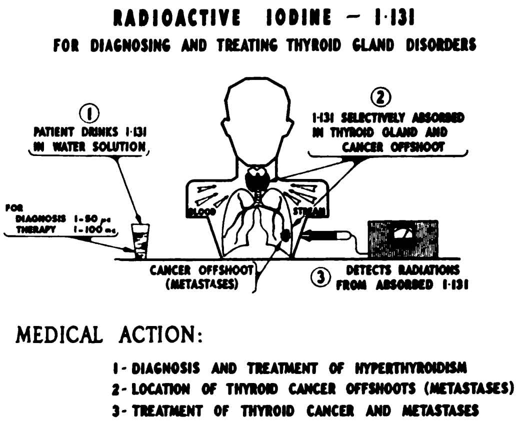


FIGURE 11.

Overactivity of the thyroid gland frequently results in the appearance of goiter as an outward manifestation. Internal consequences are much more fundamental, however, since the thyroid has a profound effect on body metabolism. The rate at which we burn up our food for energy is regulated to a great extent by the thyroid hormone. Overproduction of this hormone results in so fast a burnup that the heart is overtaxed

in pumping blood to supply the necessary oxygen. The intimate connection between thyroid and heart functions makes thyroid treatment a valuable adjunct in the treatment of angina pectoris and congestive heart failure.

Although I–131 has amply demonstrated its ability to destroy thyroid tissue, it can only rarely be used effectively against thyroid cancer. Destruction or removal of the primary cancer still leaves the metastases practically unaffected. Difficulty in inducing these to pick up I–131 is met with in therapy as it is in diagnosis, as previously discussed. Only about 10 percent of the offshoots can be stimulated to concentrate I–131 in effective amounts.

Radioiodine uptake by the metastases can be increased in three ways: (1) The physician may let "nature take its course." In this case, absence of thyroid hormone, after loss of the thyroid, stimulates the pituitary gland to produce more thyroid-stimulating hormone (TSH). The hormone rouses the cancers to take in more iodine. (2) TSH may be administered as a drug for the same purpose. (3) An extended course of treatment may be given with thiouracil, a drug which blocks iodine collection. This "starves" the cancer, so that a later dose of I–131 will be more actively collected.

Differential Turnover

The element phosphorus is necessary in all living cells so that, in time, a dose of P–32 becomes quite generally distributed throughout the body. Bone, blood-forming tissues, and rapidly growing tissue tend to concentrate it. Importance of this effect in P–32 treatment of diseases of the blood-forming system is not definitely established, but certain of these diseases respond to total body radiation, however administered. This method of treatment is illustrated in Figure 12.

Polycythemia vera, in which an excess of red blood cells is produced, has been the most successfully treated of blood-system diseases. The beta rays from P–32 do not cure the disease but repress cell formation nearly to normal, and usually can keep it there after a single large dose or repeated small ones. While X-ray and other treatments perhaps produce equally good result in polycythemia. radioisotope

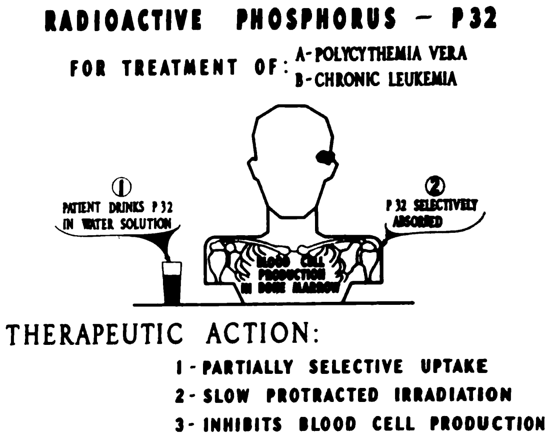


FIGURE 12.

therapy has come into wide use. It can be administered on an out-patient basis in a physician's office and radiation sickness and other side effects can be avoided.

Leukemia, in which an excess of white blood cells is produced, has not responded to P–32 therapy to as great an extent. In general, the results are quite similar to those obtained with X-rays, although the isotope treatment is usually favored because of its comparative convenience and freedom from side effects. The acute form of the disease does not seem to be affected, but satisfactory control is gained in about half of the cases of chronic leukemia.

PHYSICAL PLACEMENT

Many approaches to concentrating a radioisotope where its radiation will do the most good are based on the more direct concept of putting it there "by hand". No attempt need be made in this case to match biochemical activity of a material with that of the tissue to be treated; in fact, the concept is based on *lack* of affinity between the two. In general, such materials as gold, platinum, stainless steel, and plastics are used as sources and coverings so there will be little or no chemical reaction with the tissues or dissolving in body fluids.

Radioisotopes are used for physical placement both in solid form and as a liquid in an appropriate carrier or solution. As solids they are placed on a body surface, inserted into cavities, or implanted into the tissues. As liquids they are injected into cavities, mingled

with body fluids for transport to inaccessible parts, or injected into tissues as a dispersed source in the extracellular spaces. These various modes of application and their uses will be discussed in separate subsections.

Colloids and Suspensions

The liquid form referred to is generally not a true liquid but simply a fluid carrying tiny solid particles such as a colloid. Radioactive material which would dissolve to a true liquid would also enter the body chemistry and be lost from its desired position.

By putting the radioisotope into a form not affected by body chemicals, and suspending it in a finely divided state in a liquid which is well tolerated by the body, a number of advantages are gained. The particles remain where injected in a tissue, while the carrier is absorbed. When introduced into the blood stream, the particles are carried to diseased organs and are trapped there in the tissues. Also, when placed in a cavity, the particles deposit uniformly over the lining and remain at the surface.

Radioactive gold colloid meets many of the requirements in these applications. The beta rays emitted are short-ranged and so affect only the tissue immediately adjoining the particles. The half-life of 2.7 days allows the activity to disappear within a few days, after accomplishing its purpose, and the body tolerates the inert gold during the remainder of the person's life.

The chief disadvantage of gold colloid is that it emits penetrating gamma radiation in addition to the beta radiation. This makes it more hazardous to administer. Surrounding healthy organs are also partly irradiated as well as the local tissue. Colloidal chromic radiophosphate has come into favor in some applications, chiefly because the radiophosphorus emits only beta particles.

Other colloids are also being used to advantage, and more are being investigated. Gold colloid can be plated with silver, for example, to "fool" the body into transporting the gold radiation sources to a greater extent into the lymph channels. Yttrium chloride forms a colloid after injection into the body fluids and is generally believed to have potential importance because of the favorable half-life (2.6 days) and pure beta radiation of radioyttrium (Y–90). Other radioisotopes seem to offer special advantages in this type of therapy but remain radioactive too long for safety. These individual advantages may yet be realized as a result of research on complexing agents which may remove radioisotopes from the body when the desired therapy is accomplished.

Interstitial Injection

Direct injection of radiocolloid has provided a useful mode of treatment of many types of accessible but inoperable malignant masses. Those which are not suitable for surgery because of proximity to delicate organs, lack of definite boundary, or precarious condition of the patient are often reduced by this treatment. The tumors frequently can be given large doses of radiation which could not be administered with external X-rays without serious damage to other tissues.

This type of therapy has become routine in many hospitals in treating cases of inoperable cancer of the prostate gland. Only 5 to 10 percent of prostate cancer cases are found while still in the stage where surgical removal of the prostate and capsule can produce a cure. In about half the cases the tumor has invaded its surroundings, and it is in this class that interstitial injection of radiocolloid has been used with good effect. In the remaining cases, spread has occurred to distant areas, usually bone or lungs, and the radioactivity carried to these sites by the blood stream is not sufficient to produce a significant effect.

Encouraging results have been obtained where the colloid was used before metastasis occurred. Users of this technique have stated that the most striking effect is the rapid regression in prostate size, experienced in very nearly all cases. In 7 to 10 days a large nodular prostate can shrink until it is barely detectable.

Involvement of the lymphatic system frequently occurs in cases of cancer because cells and tissue fragments separated from the malignant mass are drained off along the lymph channels. Removal of infectious agents

and broken-down cells is a natural function of the lymph system. This function, unfortunately, aids in the spread of cancer because the cancer cells start new growths where they come to rest. This most frequently happens at the lymph nodes, the collecting points of the system, which are usually distant from the cancer and at inaccessible locations. An advantage of radiocolloid therapy in such cases is that the radioactive particles are often drained off in the same way and become lodged at the same points.

Both surgery and X-irradiation, when they fail in cases of cancer of the cervix, do so primarily because of residual cancerous growth in the lymph nodes and the adjoining tissues. Radiogold colloid has demonstrated its ability to reach the lymph nodes for localized destruction after injection near the tumor mass. It may be used as an adjunct to other therapy in cervical cancer cases.

Intravenous Injection and Clearance

When a colloidal substance is introduced into the blood stream a somewhat similar result is accomplished. The reticulo-endothelial system, a group of specialized cells widespread through the liver, spleen, lymph glands, and bone marrow, clears particles and debris from the blood. Radiogold colloid, when injected into a vein, is caught in this system and thus furnishes a means for treating its diseases. Chronic lymphatic leukemia, for example, responds to this treatment about as often as to drugs and X-rays. Hodgkin's disease and lymphosarcoma are also treated in this manner.

Distribution within the body depends partly on particle size. A degree of control can thus be realized through choice of an appropriate size. Extremely small particles of gold, measured in millionths of an inch, are produced from a solution of a radioactive gold compound. Slight alterations in the chemical technique can give a range of sizes. Larger particles may be obtained by depositing the radiogold on suspensions of finely divided charcoal.

An entirely different distribution is obtained with the larger particles. These, when injected into the blood, are caught in the fine capillaries of the lungs, whereas the smaller particles of a gold colloid pass through and concentrate in liver and spleen. Cancer growths distributed throughout the lung, as a result of blood transport from a distant primary cancer, can thus be given local radiation treatment by the particles blocked at the scattered sites. This type of therapy is relatively new and may result in useful treatment when the possibilities of controlling placement and distribution have been further explored.

Intracavitary Injection and Instillation

Radiocolloids, being in fluid form, are well suited for placement in body cavities to irradiate cavity linings. Beta radiation from only the outer particles can reach the tissues without being absorbed in the liquid, so that the effect is that of a thin radioactive coating. Moreover, the particles are rapidly deposited upon the surface itself and are engulfed in the cells. Only about 1% of the particles escape through lymph channels to the blood and thence to liver, spleen, and marrow, so that undesirable systemic effects of the treatment are usually negligible.

This technique, illustrated in Figure 13, is being used in about 250 hospitals in the control of fluid accumulation in the abdominal and chest cavities of cancer patients. Often pain or disturbance due to fluid pressure on adjacent organs is the only awareness the patient has of

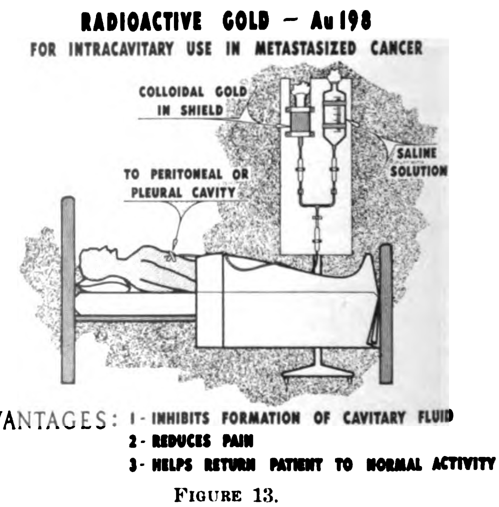


FIGURE 13.

his disease. Irradiation of the cavity lining reduces or prevents the fluid formation, and can make his existence tolerable while treatment of his disease is attempted. Reports by those using this technique indicate that relief from symptoms can be obtained in approximately 50 percent of the cases. The general opinion is that it is best suited to cases in which the cancer is growing slowly and the accumulation of fluid is the most important symptom.

Radiocolloids have also been injected into cavities as a preventive measure rather than as a treatment. Radiogold is sometimes used in this manner when a cystic cancer of the ovary is removed. In this operation, there is a possibility that some of the contents of the cyst will be released into the abdominal cavity. Introduction of the radiogold seems to decrease the probability that the cancer "seeds" will grow.

Cancer of the lung almost always involves the adjacent lymph nodes. Radiogold colloid has frequently been put into the lungs, by injection or tube, for drainage to these sites. The slowness of the drainage, however, is a disadvantage of this technique since the gold radioactivity is practically spent in the 10 or more days before optimum concentration occurs. This period has been reduced to about 5 days by coating the radiogold with silver.

A still greater improvement has been achieved, in experimental work with dogs, by injecting the gold colloid into the wall of the bronchus, or windpipe. From there it has only a short distance to travel and accumulates effectively in the lymph nodes within 3 days.

Too intense irradiation of a localized area of tissue is avoided wherever radioisotopes are applied. If tissue is killed faster than its fragments and breakdown products can be disposed of through the lymph and blood, toxic substances are formed and released into the system as in gangrene. Too intense a dose of radiocolloid put into the quite radiosensitive lung, in an attempt to achieve adequate transfer to lymph nodes, needs to be avoided. However, it has been suggested that a lobe of the lung can be used simply as a transfer point for part of a heavy dose, when the lobe is about to be surgically removed in any event.

The lining of the bladder has also been treated by radiocolloid instillation, or introduction by tube. Filling the cavity with the fluid allows particle sources of beta radiation to surround each tiny papilloma or protuberance from the wall. After sufficient time for effective action, the cavity can be drained.

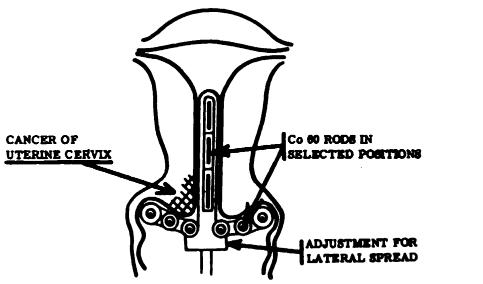
Intracavitary Insertion

Radium has long been used in devices specially designed for insertion into body cavities. This mode of radiation therapy has been greatly extended by the greater availability, economy and, in many cases, effectiveness of the newer radioisotopes.

Cobalt 60 is roughly equivalent to radium in this type of application and devices designed to hold the one are frequently used for the other. Figure 14 shows a simplified illustration of such a device. Various radiation patterns can be produced by using selected intensities and positions of the radioactive inserts.

RADIOACTIVE COBALT – Co 60

FOR INTRACAVITARY OR EXTERNAL APPLICATORS



PERMITS WIDE VARIETY OF APPLICATORS

READILY AVAILABLE AND INEXPENSIVE

ALLOWS LARGE INVENTORY OF SPECIAL SOURCES

FIGURE 14.

Balloon catheters, also, are used for internal irradiation of body cavities. After insertion into the bladder or uterus, for example, they can be inflated to expand the organ and smooth out the folds and irregularities of its lining for uniform irradiation. Fluids attempting to enter the cavity while the device is in place are drained off through a central catheter. One form of balloon catheter may be filled with a liquid. Since the liquid does not contact the tissues directly, it can be a solution containing

any radioisotope with the desired radiation characteristics. In a second form, the catheter carries a small radioactive source at the center so that, when the balloon is inflated, the cavity walls will be properly spaced from the source for uniform irradiation.

Interstitial Implants

The insertion of radium needles and radon seeds into cancer tissue is a well-established mode of treatment. Here, again, the technique has been extended and improved with radioisotopes. Cobalt 60 wire is the material most used for this purpose. It can be made much more radioactive than radium, so that only very thin wire need be used. This is encased in an inert, nonradioactive sheathing, such as stainless steel, which absorbs the beta radiation but does not hinder the gamma rays and is unaffected by body chemicals. The encased wires are cut to the desired lengths and can be bent to shapes appropriate for the tissues or growth to be treated, although they usually resemble straight, rather thick sewing needles. In use they are inserted in a predetermined pattern to give the desired radiation field and are removed when a specified radiation dose has been delivered.

Both Iridium 192 and Tantalum 182 are used in the same manner, with certain advantages and disadvantages when compared to Cobalt 60. Both have a greater neutron absorption and so can be given a higher activity in a reactor. On the other hand, they have much shorter half-lives (Ir–192, 74 days; Ta–182, 111 days; Co–60, 5.3 years) and require reactivation from time to time.

Implants also take the form of short lengths of radioactive gold wire encased in inactive gold tubing. These are comparable to the widely used radon seeds and, because of the short half-life of radiogold, can be left in the tissues permanently. The encased wire can be conveniently cut in the operating room to lengths providing the required amount of radioactivity. The simple act of cutting seals the ends sufficiently against beta-ray leakage. The gold seeds have entirely supplanted radon at some hospitals.

A unique form of implant has been developed in which short lengths of either the radiocobalt or radiogold wire are alternated with inactive aluminum lengths within very thin nylon tubing. This radioactive "suture" is sewed into the tissues in a configuration designed to give the best radiation pattern.

An even more recent development makes use of copper-covered iridium wire for this purpose. Before irradiation, the wire is slipped into a sheath of thin copper tubing, to absorb the beta particles, and cut into 3- or 4-mm lengths. Radioactivity induced in the copper is short-lived and disappears before use. The lengths are irradiated and then the desired number, say 10 or 12, are spaced at 1-centimeter intervals in nylon tubing, with 3 or 4 inactive aluminum pieces as a continuation at both ends. The tubing is compressed between the wires to maintain their spacing. Enough tubing is left at one end to allow the radioactive portion to remain in a shielded container while the surgeon places his needles in the desired pattern in the tissues and threads the free end of the tubing into the first needle. A minimum of time is then needed to draw the active portion into position. The aluminum markers indicate how many centimeters the end sources are below the surface.

Another implantation technique is reported to be ready for clinical trial. This involves the use of beads, less than a millimeter in diameter and of carefully predetermined radioactivity, for implantation in brain tissue. Radioactive gold, palladium, and yttrium have been used as these sources. Since beta particles travel only a very few millimeters in tissue, a very small spherical volume can be given a predetermined irradiation.

Topical Application

The very short range of beta particles from certain radioisotopes has been advantageous in surface applications. Many skin conditions, including warts and benign and malignant tumors, are treated with X-rays but only the very softest, or least penetrating, of these rays can be relied on to affect the outer layers without damage to deeper structures. In contrast, the beta radiation from radiophos-

phorus, for example, has an average penetration of only about one millimeter and cannot reach the underlying tissues.

Plaques of many types have been devised for holding concentrated or dispersed beta-ray sources next to the skin. The simplest form is obtained by soaking a piece of absorbent paper in a radioactive solution and holding it to the skin with adhesive tape. Another simple type is obtained by incorporating a finely divided radioactive material into a plastic substance which can then be molded to the contour of the surface. Actual contact of the radioisotope and skin, in these cases, is prevented by a thin wrapping of Cellophane or the like.

Ophthalmic Applicators

A variety of devices have been designed for beta irradiation of eye lesions. These employ the same radioisotopes as in the surface plaques just described and have the same effect—in fact, they are often used in treating skin conditions. They usually are designed as hand-held instruments with a radioactive tip, and are frequently provided with a shield to protect the physician's fingers. More than 230 of these applicators are in service in treating benign and malignant lesions of the eye. The beta-emitting isotope Strontium 90 is most frequently used as the source.

Nasopharynx applicators are quite similar but adapted, as the name implies, to use in treating pathological conditions of the upper air passage. Strontium 90 has been in favor for this use also, with Cobalt 60 occasionally providing a gamma-ray instrument for special conditions.

TELETHERAPY

Distance therapy by means of a gamma-ray beam from a concentrated pellet of radioisotope is a direct outgrowth of teleradium and X-ray treatment. Since the beam is directed through the body to the cancer or other growth to be eradicated, an important consideration is the amount of damage to healthy tissue. Certain radioisotopes have shown a superiority to X-ray equipment in this respect, because the whole of their radiation has the same energy or penetrating power. In an X-ray beam a large range of energies are present and much of the beam must be filtered out in eliminating the portion most harmful to overlying tissues. To obtain a useful beam with radiation as penetrating as that from Cobalt 60, very special and expensive X-ray equipment in the 2-million-volt range is required.

A Cobalt 60 unit is basically a small piece of the radioactive metal at the center of a large ball of lead or other heavy shielding. A passageway for a beam of gamma rays from the cobalt is blocked by a shutter of movable shielding when not in use. This basic unit, to be useful, must be supported in such a way that the beam can be directed as desired. Further details of control are added according to the proposed use and budget allowance. Thirty or more machines are now in use in the United States. They differ in the degree of complexity introduced by positioning controls, timing mechanisms and, in some instances, even electronic computers to direct the movements throughout a treatment.

The machines fall into two classes depending upon the source strength and, therefore, the amount of shielding. The "hectocurie" units, with source strengths of a few hundred curies, can be light enough to roll from place to place. The "kilocurie" units have sources of a few thousand curies and are permanent installations.

The ruggedness and comparative simplicity of the source holder and shielding gives the basic unit a high degree of maneuverability. The advantages of "rotational" therapy, for example, can be obtained by swinging the beam source entirely about the patient, as in the kilocurie unit illustrated in Figure 15, with the beam continually directed at a tumor. A heavy dose of radiation can be delivered to a small volume in this way without overdosing any one part of the skin or healthy tissue.

The basic principle in placing the source at a distance from the patient, when internal structures are to be irradiated through overlying tissue, is a geometrical one. The rays spread out in straight lines from the source so

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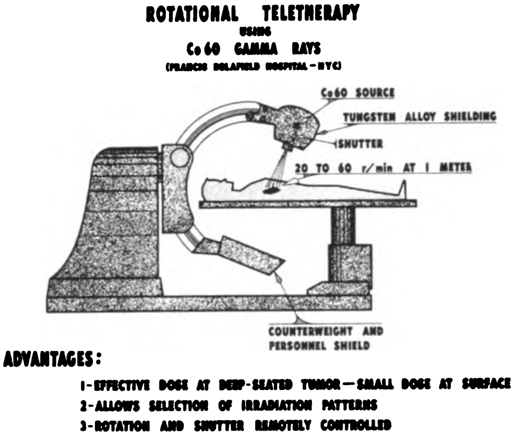


FIGURE 15.

that an area of a given size receives less radiation as it moves away. In mathematical terms, the intensity varies inversely with the square of the distance. Therefore, with a very near source the intensity at the skin is much greater than at the more distant tumor. However, with the source a few feet away the tumor-to-skin distance makes little difference and a radiation dose can be given to a tumor without a much larger dose going to overlying tissues.

With the exception of radium units and one Cesium 137 unit all of the 30 or more teletherapy machines in operation are using Cobalt 60. About 15 other hospitals have machines in various stages of completion but are awaiting their turn for cobalt being activated at the National Reactor Testing Station in Idaho.

Cesium 137 offers some advantages over Cobalt 60 as a teletherapy source, chiefly because of its much longer half life (33 years vs. 5.3 years) and the reduced amount of heavy material needed to shield its less penetrating gamma rays. This isotope, however, has not been available in large quantities, except for the 1540-curie source prepared at great effort for the one unit mentioned above. The new fission product separation plant, mentioned later under Available Materials and Services, is expected to produce kilocurie sources suitable for teletherapy.

NEUTRON-CAPTURE THERAPY

A quite different technique is being developed, especially for the treatment of brain tumors, in which a stable isotope is made radioactive *after* biochemical concentration in a tumor. The stable boron isotope B–10 in the form of a borax solution, for example, is administered to a patient. Impairment of the blood-brain barrier by the brain lesion allows temporary concentration of the boron. The head is then exposed to a beam of reactor neutrons. Boron 10 absorbs neutrons much more readily than the other elements present, and each absorbing atom emits an alpha particle which ionizes heavily during its very short travel. Localized destruction of tumor tissue is thus accomplished.

Agricultural Studies

The frontiers of farm science and land development must be pushed forward at an ever increasing rate to provide for world population growth and to improve living standards. Food production is not increasing as fast as population demands. World population is increasing at the rate of about 1 percent or over 20,000,000 persons per year. Reliable estimates indicate that over half of the more than two billion people in the world today do not get enough to eat.

To keep food production in pace there must be ever increasing production from the land and this advance must be based upon the work of plant and animal scientists.

All over the country agricultural research is being stimulated through the use of radioactive and stable isotopes. These new tools are unlocking the secrets of the growth of plants and animals and the scourges that injure or destroy them. Most of these isotope uses are related to the fate of metabolites and non-metabolites in plant and animal systems. The major applications of radioisotopes to agricultural problems have been concerned with soils and fertilizers, photosynthesis, entomology, and animal and plant nutrition.

The hundreds of agricultural uses of radioisotopes are here separated into several types of uses and only a few representative examples of each are discussed.

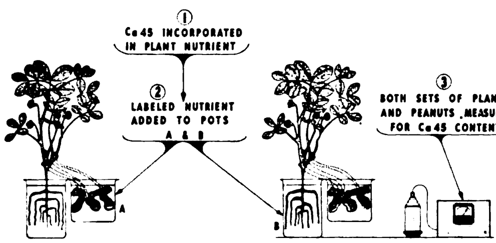
PLANT STUDIES

Metabolism and Translocation

The movement of mineral nutrients in plants is being studied at several institutions. Radioisotopes of phosphorus, sulfur, calcium, copper, molybdenum, and zinc are being used to investigate important plant nutrition problems. Radiotracers are being used to determine the path, rate of entry, and movement of materials in plants, the mechanism of such movement, and to trace steps in the mechanism of transfer of ions from the environment to the plant cell interior. Tracing elements through living plants was impossible before radioisotopes became available.

As illustrated in Figure 16,radioactive calcium has been used successfully to study the uptake of calcium (the element supplied by liming) by the root and fruit in the peanut plant. This investigation showed that although calcium is absorbed in the plant by both the fruit and root, absorption by the roots alone is not sufficient for fruit development.

RADIOACTIVE CALCIUM – Ca 45
FOR STUDYING PLANT NUTRITION



INDICATES:
1 - ROOTS SUPPLY INSUFFICIENT CALCIUM FOR FRUIT GROWTH
2 - LOCATION OF GREATEST ABSORPTION
3 - ABSORPTION DURING EARLY FRUIT GROWTH

FIGURE 16.

Iron 55 has been used to study effects of acidity and action of charged particles on soils, and to trace soil nutrients in the uptake and translocation of iron by sorghum plants. Iron 55 and Zinc 65 have been used to determine factors influencing uptake and distribution of inorganic elements within plant tissues and their use in organic compounds synthesized within the plant. Carbon 14 has been used to study translocation of labeled organic materials in most of our economically important plants.

Uptake of Fertilizers

The most extensive use yet made of isotopes in agriculture has been concerned with studies on the uptake of fertilizers. This was one of the first and most important uses in agriculture. Now, even after 8 years, fertilizer uptake studies are still yielding valuable infor-

mation. With radioactive tracers it is possible to study not only commercial fertilizers, but green manures as well. These applications are illustrated in Figures 17 and 18.

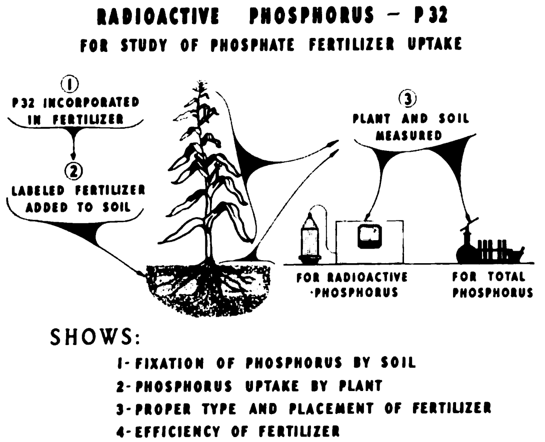


FIGURE 17.

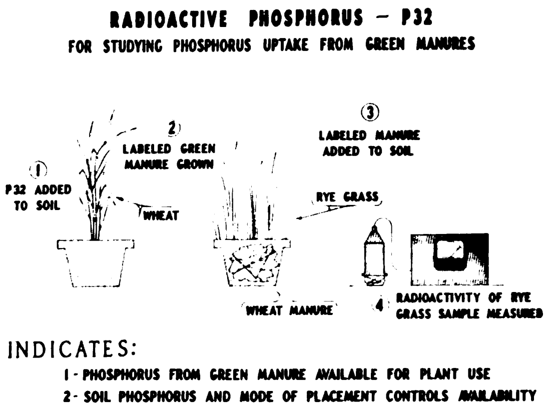


FIGURE 18.

Although most of the investigations are designed to determine the proper type, placement, and efficiency of various fertilizers, the data obtained provide many other answers since the studies can be carried out under a wide variety of soil and climate conditions. American farmers are spending more than a billion dollars a year for commercial fertilizers, and isotopes research has found many ways to get greater returns in crop yields with this money.

With radioisotopes, it is possible to tag a certain material such as phosphorus in the fertilizer, and tell how much moves into the plant. The effectiveness of different methods of placement of the fertilizer such as below the seed, broadcast, or foliage application can be easily compared. In the past, requirements of a crop on a particular soil for a specific fertilizer usually have been measured by crop yield, but variations in rainfall, temperature, disease, and other factors also affect yield and confound the evaluation of the fertilizer. Through the use of radioisotopes many years are being saved in evaluating fertilizer materials and methods of application, and sound conclusions about fertilizer practices are being drawn.

The capacity of the soil to supply a plant nutrient can be measured by adding a labeled fertilizer as a partial source of the nutrient to the growing plant. The plant will draw upon both the natural supply and the added fertilizer in proportion to the availability of each. In some soils, most of the plant nutrient will come from the added fertilizer, in other soils most of it will come from the nutrients already present in the soil. The isotope dilution analysis is used to obtain this information. Thus the plant itself, which is the best judge of availability, is used to give the answer.

Although measurement of crop yield is satisfactory and in some cases preferable, the new techniques permit an evaluation under varying field conditions and at any stage of the plant's growth through the season.

Through the use of isotopes, it has been proved conclusively that plants absorb nutrients not only through the roots but also through the foliage, the fruit, the twigs, the trunk, and even the flowers. Comparative uptakes of Phosphorus 32 are illustrated in Figure 19.

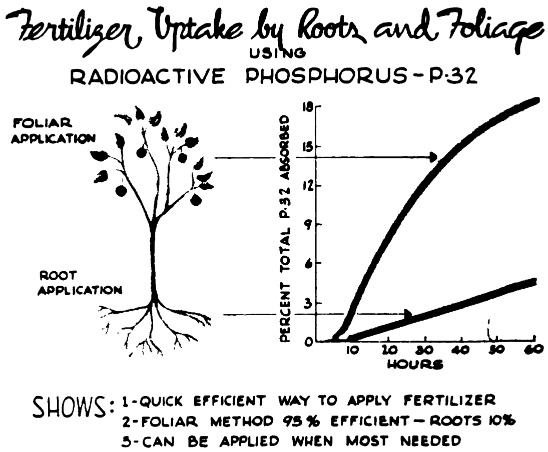


FIGURE 19.

Tracer studies show that certain plant nutrients applied to the leaves in soluble form result in as much as 95 percent uptake by the plant. Plant nutrients applied to the soil often show no more than 10 percent uptake.

Work in California and in Oregon showed that spraying dormant trees with fertilizers improved the growth of the fruit the next year. It has been shown that within 24–48 hours, even in mid-winter and at below freezing temperatures, radiozinc movement in the branches can be traced 18 inches to 2 feet above the point of application. Furthermore, the nutrient tends to accumulate near the buds. Thus the entry of nutrients into dormant branches is proved and the value of spraying fruit trees with zinc in the dormant season is established.

Similarly, the radioisotope technique shows that a leaf is a very efficient organ of absorption. Experiments prove that the nutrient material moves in from any leaf surface both night and day.

If leaf feeding is compared with soil feeding radioisotopes demonstrate that nutrients supplied to roots move upward in the plant. If applied to the leaf the nutrient moves downward in some plants at the rate of about one foot an hour. When applied to a middle leaf the nutrient moves both ways very effectively. Also learned during these studies is the fact that certain parts of a plant need specific nutrients at different times.

When seeds form in fruit, radioisotopes show that phosphorus concentrates immediately in the seed. In the case of the apple both phosphorus and magnesium concentrate in the seed when it is developing. This explains why a magnesium deficiency appears in the foliage in summer when seeds are drawing magnesium from the leaves.

Studies with radiocalcium have shown that foliage application does not result in movement of this nutrient to root sections. This is of considerable importance, for example, in growing strawberries. Calcium applied to the foliage of strawberry plants would not move to the roots. Daughter plants nourished only by roots might therefore starve to death for lack of calcium if the material is available only through the leaves. Calcium must be applied to the soil to reach the entire plant including the roots.

Urea applied to the foliage is being used very freely by orchardists and vegetable crop specialists. The urea molecule has two groups of nitrogen atoms in addition to one oxygen and one carbon atom. Since no suitable radioisotope of nitrogen exists the molecule is made radioactive by using radioactive carbon. (It can, however, be traced by a heavy isotope of nitrogen, stable N–15.) When urea is applied to a plant the enzyme "urease" acts on the molecule and splits it. The groups containing nitrogen combine with hydrogen in the plant moisture to give ammonia which moves into the plant. The radioactive carbon and the oxygen from the plant moisture combine to give radioactive carbon dioxide. By counting the radioactive carbon dioxide that is given off, one can obtain an absolute measurement of the use of nitrogen from the urea applied. This test has given valuable information on the ability of different plants to use this compound.

Soil Fertility

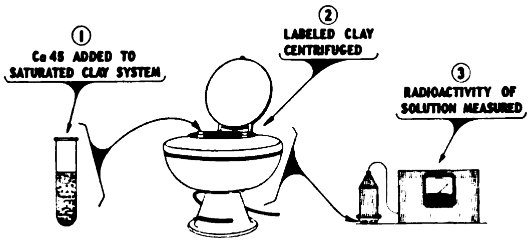
Of major concern in agriculture are the amounts of naturally occurring nutrients in soil, their exchange between the soil, the soil solution, and plant roots, and their availability to plants.

Maintenance of soil fertility is the main objective of soil management. Soils of the United States Corn Belt are fertile, but their continued ability to supply adequate potash (potassium) to corn has been questioned. The capacity to supply potash can be measured with radioisotopes. Unfortunately, one cannot use a radioisotope of potassium in field studies for it has none with long enough half-life. However, radioactive rubidium, which behaves chemically very similarly to potassium, can be used and follows along with potassium as a tracer. These studies are yielding valuable information on soil maintenance questions.

A tracer study directly related to soil fertility is the use of radioactive calcium in measuring the kinetic exchange of this element in various types of clays. The radioisotope tracer tech-

nique, illustrated in Figure 20, is particularly suited to measurement of exchange between ions of the same element. This study shows that calcium exchanges readily.

RADIOACTIVE CALCIUM – Ca45
FOR STUDYING KINETIC EXCHANGE IN CLAYS



ADVANTAGES:
1- MEASURES EXCHANGE BETWEEN IONS OF SAME ELEMENT
2- CONFIRMS KINETIC EQUILIBRIUM

FIGURE 20.

Calcium 45 has also been used to study the absorption of calcium by alfalfa and other legumes as influenced by soil reaction, amount of exchangeable calcium, degree of calcium saturation, presence of manganese, iron and aluminum, and method of application.

Likewise, Phosphorus 32 is used to study exchange reactions of inorganic phosphorus between solutions and mineral surfaces in soils and synthetic calcium phosphates, and to determine the contribution of phosphorus in manures to the fertility of the soil.

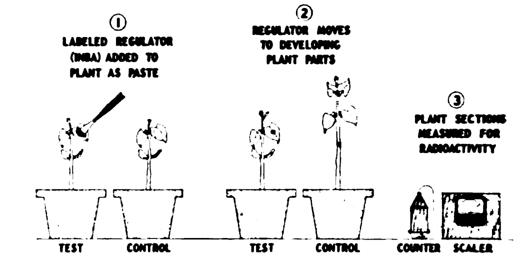
Carbon 14 has been used to study decomposition rates of organic materials in soils and their availability as nutrients to plants. Radioisotopes of potassium, calcium, and rubidium have been used in the laboratory to study exchange equilibria reactions of these elements in soils. In other laboratory studies, Sulfur 35 and Calcium 45 have been used to determine the rate of leaching of these elements through columns of soil.

The radioisotope technique opens new vistas in basic research on soil fertility. It adds to the precision and reliability of measurements of importance to agriculture. It does not make obsolete other current research methods but rather supplements them as a very useful new tool.

Action of Growth Regulators and Herbicides

Radiosotopes are used to study the behavior and action of plant-growth regulators and herbicides. These investigations are concerned primarily with how these materials act on metabolic processes. The method, illustrated in Figure 21, is so specific it can show how a regulator is translocated to developing parts of the plant. Further, it is so sensitive that it indicates accumulation of as little as a millionth of a gram.

RADIOACTIVE IODINE – I-131
FOR STUDYING MOVEMENT OF PLANT GROWTH REGULATORS



INDICATES:
1- DETAILED PATHWAY OF TRANSLOCATED REGULATOR
2- REGULATOR TRANSLOCATED TO DEVELOPING PARTS OF PLANT, PROBABLY INTACT
3- ACCUMULATION OF REGULATOR IN MILLIONTHS OF GRAM RANGE

FIGURE 21.

Growth regulators can speed up or slow down the growth of plants. Advancing the date for maturing of crops, in some cases, can mean thousands of dollars of added profit in the market place. Radioisotopes are helping to find better growth regulators.

In the war on weeds radioisotopes have been called upon to help explain the complicated actions of herbicides. It has been estimated that crop losses due to weeds alone amount to at least 5 billion dollars annually. Weed plants take water and nutrients meant for crops and are carriers of both animal and human diseases. Their presence increases the cost of tillage by almost 50 percent.

Certain chemicals can kill some plants and spare others. The best known herbicides now in use are the phenoxyacetic acid derivities known popularly as 2,4-D and 2,4,5-T, produced in 1954 at a rate exceeding 60 million pounds.

The action of herbicides on the alligator weed has been investigated with C–14-labeled 2,4-D. Through this study valuable information was gained on possible new materials for combatting the weed.

It has been shown that bean plants readily absorb the radioactive 2,4-D, and radioactivity has been found in the various parts of the plant. This absorption into edible plants is important, of course, because of possible effects on the plant and on persons who eat the beans. In a continuation of the study, two radioactive compounds in addition to unchanged 2,4-D were found in an extract of the stems of bean plants treated with labeled 2,4-D. This led to further work on metabolism of 2,4-D in 2,4-D resistant plants and to studies of the absorption and metabolism of radioactive 2,4-D by crops such as corn and wheat.

Plant Diseases and Fungicides

Plant diseases cause an estimated annual agricultural loss of approximately $3 billion. Old as well as new diseases sweep the country from time to time.

Some plant diseases are annihilating. Cereal rust may destroy up to two-thirds of the crop of wheat and oats in extensive areas. Potato blight can almost completely destroy potatoes in the field or in storage. Many other diseases are debilitating or disfiguring. They may cause pealing, root rot, wilt, scab, and various other disorders. Most plant diseases are insidious because of the relative invisibility of the disease organisms.

Radioisotopes are of great value in studying plant diseases and devising means for their control. Carbon 14 has been used to study metabolic changes in tobacco plants induced by virus infections, mealy bug wilt of pineapple, and effects of the virus of "little cherry" disease. Sulfur 35 has been used to measure the difference in absorption of sulfur by parasites and the host in plant diseases caused by fungi. Phosphorus 32 and Calcium 45 have been used to compare absorption and movement of phosphorus and calcium in pole-blighted and healthy western pines.

Wheat stem rust and most other rusts can be controlled if plants can be dusted often enough with sulfur. But to dust 70 million acres of wheat in the United States with the minimum amount of sulfur that would be effective in years when weather favors rust would require nearly 2 million tons of sulfur. Cheaper fungicides, therefore are badly needed and radioisotopes are helping to find them.

Work has been done on methods for tagging fungal spores with radiocarbon. The effect of radiocarbon upon the growth and genetics of the tagged organisms also has been investigated.

In testing the toxicity of chemicals to fungus spores, chemical methods of determining the quantity of uptake by the spores are impractical because of the minute amounts involved. With the availability of radioactive isotopes, quantitative uptake of the toxic chemical on a spore weight basis can be carried out quite easily.

Isotopes also make possible study of the relationship of several toxicants and the replacement of one material by another in fungus spores. Spores of various species were found to act quite differently in their affinity for various toxicants.

Other types of plant disease studies with radioisotopes are illustrated in Figure 22. They are concerned with the proper balance of normal metabolic processes. In the study of molybdenum, an essential mineral for plant nutrition, it can be determined by the tracer technique what concentration of the element blocks iron uptake and causes chlorosis (an iron deficiency) as well as the mechanism of the block. Since the amounts of molybdenum and iron involved

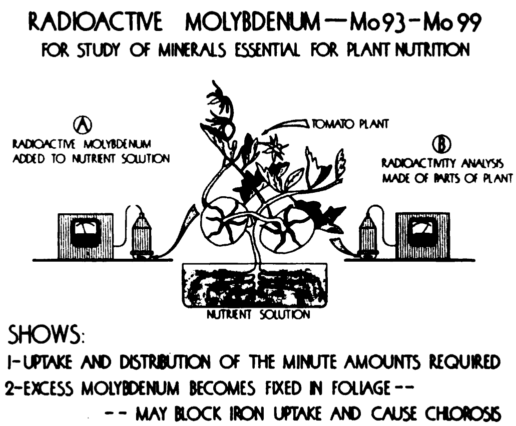


FIGURE 22.

in this plant disorder are very small, the sensitivity of the tracer technique is of particular advantage. Iron 55 and 59 also have been used to follow iron metabolism under conditions conducive to chlorosis.

Radiation Effects and Genetics

The science of radiation genetics may have a fundamental effect upon agriculture since it offers promise of developing new strains of hardy, disease-resistant plants. Natural mutations, or changes in the germ cells which transmit inherited characteristics, occur spontaneously although at a very slow rate. Ionizing radiation causes them to occur much faster.

Early genetical studies used X-rays and radium, but the work was on a limited scale. Reactor-produced radioisotopes provide the geneticist with new tools that greatly facilitate plant breeding.

With better radiation sources, radiation genetics is being studied from two different points of view. The first approach is designed to give a better understanding of the science of radiation genetics and consequently of genetics itself. The second is a much more practical approach to the use of radiation for the solution of specific agricultural problems.

By means of fundamental studies, plant scientists have been able to define accurately the way in which radiation should be given to a plant, the biological conditions which must be fulfilled, the type of radiation to use, the results that may be expected, as well as a great many other factors necessary for an intelligent approach to the problem.

Such fundamental studies have produced evidence that some radiation-induced mutations are desirable changes. As a direct result of these studies, scientists recently have applied their findings to the solution of specific agricultural problems. One of the most spectacular of these results is the development of rust resistant oats by means of neutron irradiation. After only one and one-half years, a small amount of rust resistant oat seeds was obtained. Conventional plant breeding methods might have taken 10 years to produce this result, at considerably greater expense.

Disease resistance is by no means the only desirable characteristic which can be induced by radiation. The most striking example so far of the induction of other characteristics is illustrated by work in North Carolina. Irradiation has produced peanut plants which have about 30 percent higher yield per acre, a size and shape better adapted to mechanical harvesting, and better resistance to common leaf spot diseases.

Attempts are also being made to develop shorter corn plants which provide a greater yield of grain per stalk. In Nebraska there is a program to develop a winter hardy barley.

Many important crops, such as apples, are not normally propagated by seeds but are reproduced by means of branch grafts. Several types of plants and vines are being grown in gamma-ray exposure fields. Branches are removed from time to time and grafted to normal host plants in radiation-free areas. It is expected that these will produce many abnormal branches bearing new types of fruit.

Nature continues to produce new and virulent strains of plant-disease organisms. Radioisotopes have proved to be very useful in determining the potential virulence of some types of fungi. This is done by exposing a disease fungus to radiation in order to speed up the natural mutation rate. In this way it is possible to gain some insight into what types of new diseases may occur naturally in the future.

The degree to which plant disease can be overcome will depend on how well possible future diseases are understood. Thus, much basic research is required and in many cases radioisotopes provide the only key.

Moisture Distribution and Cloud Seeding

Droughts have a vital economic effect upon agriculture. Any new information about weather in general and rainfall in particular is of great importance to the farmer. The versatility of the radioisotope technique has made it a useful new tool in this field.

For most efficient use of natural precipitation, particularly in western states, it is helpful to know the amount of precipitation both as it falls and as it is stored in snow packs in the mountainous areas. Without this informa-

tion, proper preparations cannot be made to store a portion of the water in lakes and reservoirs for later use when it is most urgently needed. Commitments for irrigation water supplies as well as hydroelectric current are made on the basis of snow measurements.

Snow-survey and precipitation-gage data give only limited information because of the inaccessibility of many important watersheds during the winter months. However, the use of radioisotopes allows reliable and economical methods for measuring and telemetering information on the amount of water stored in mountain snow packs. A snow gage utilizing Cobalt 60 has been developed and integrated with a telemetering system. The application is illustrated in Figure 23.

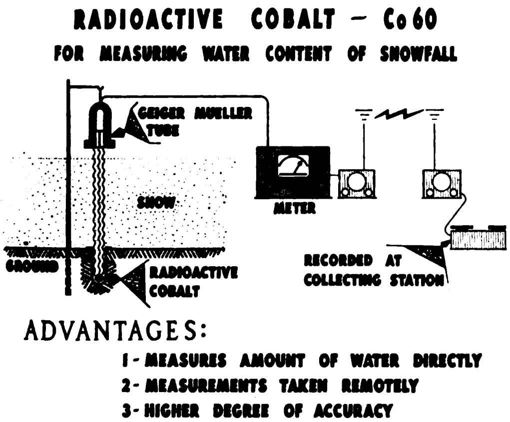


FIGURE 23.

Radiosilver has been used to study cloud seeding, which had undergone extensive testing as a means of artificially producing rainfall. The experiments, conducted in Oklahoma, employed Ag 111 in proper combination with stable silver iodide for introduction into the atmosphere. The tagged AgI crystals were used to trace the concentration and distribution of such crystals in the atmosphere both vertically and horizontally and under specific atmospheric flow conditions. The precipitation believed to have been induced was analyzed. This more accurate method of measuring gave knowledge of AgI concentration and distribution in the atmosphere and in possible precipitation from seeded clouds.

Radioactive rubidium has been used on Hawaiian sugar plantations to study water flow and distribution during irrigation. In several field tests water inflow measured by the rubidium technique agreed very closely with water measured by Parshall flumes. These tests are pointing out weaknesses in the present system of timing water flow and volume of water used. With fuller data, changes in irrigation methods can be scheduled to obtain a better distribution of water.

Cobalt 60 and Cesium 137 are being used also as sources of gamma rays for measuring soil moisture on Hawaiian sugar plantations. There are obvious advantages in having absolute moisture values continuously available without disturbing the soil. Readings can be taken at several steps across the main root system.

Cesium 137 is being used in a detailed study of the relation of soil water to photosynthesis. Experiments are being carried out with potted plants and the soil moisture is measured by the gamma-ray method. The tops of the plants are sealed in glass chambers so that the rate of uptake of carbon-dioxide from the air can be followed continuously. Exact time relations between plant wilting and photosynthesis are being sought.

Studies of efficient use of fertilizer also have provided information on moisture availability to plants. Tagged fertilizer placement studies indicate the time and depth at which supplemental irrigation is most required. Such irrigation is important in production of high-acre-value crops such as tobacco, even in areas of high annual rainfall.

Root Growth

To achieve higher yields from plants, a better understanding of root systems and their rate of growth is important. An insight into this important aspect of plant growth is gained during fertilizer uptake and soil fertility studies with radioisotopes.

For example, tracer studies show that corn plants which have extensive root systems during maximum growth cannot get a major share of the phosphorus from a surface application made at planting time. The roots are predominantly below the plow depth when the corn is maturing.

Therefore, radioisotopes show that the crop feeds largely on phosphorus already in the soil.

Other interesting points observed in tracing fertilizer include the comparatively shallow feeding of cotton plants and the heavy uptake of nutrients from immediately beneath the peanut plant during the first 7 weeks of growth. Research of this kind is leading to a better understanding of the volume of soil utilized by various crop plants. In the soils of the Southeast, which are naturally low in fertility, plants are usually expected to subsist on nutrients supplied in the top 6 inches, or plow depth. It may be possible to raise the ceiling on yields by providing a deeper zone of nutrients more in keeping with the needs of the plant. If heavy rooting could be induced in a number of crop plants to the depth of one additional foot, the bad effects of relatively brief droughts would be materially reduced.

In studies of root system growth radioactive phosphorus was placed in the ground at various depths and positions around the base of the plants. The appearance of radioactivity in a plant indicated that roots had reached the fertilizer and permitted making a detailed pattern of root growth as the plant grew. Information was obtained on how much each zone of the root system contributed to the phosphorus nutrition of the plant.

Radioisotopes will certainly play a prominent role in further fundamental research on rooting characteristics in relation to soil properties.

Photosynthesis

Photosynthesis is the process through which green plants make food out of air, water, and the radiant energy from the sun. It was not until 1940 that anything definite was shown about the role of water in the process. Oxygen was known to be evolved but its source was in considerable doubt. At that time, scientists in California, using water labeled with stable Oxygen 18, definitely established water as its source

Scientists in England were successful in determining the next major stage in photosynthesis. It was found that if the leaves of a plant were ground up, and thereby the process of photosynthesis as a whole destroyed in the plant, the individual bits of green coloring matter from the plant would still carry out the reaction of evolution of oxygen and transfer of hydrogen when placed in water and subjected to sunlight.

In 1946, when Carbon 14 became available in large quantities from Oak Ridge, researchers at a score or more universities began investigating the chemical reactions of carbon dioxide after hydrogen is transferred into the system. This work led eventually to the discovery of later steps in the process.

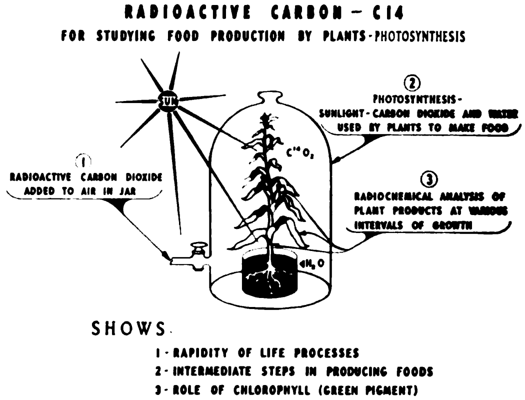


FIGURE 24.

As in many life processes, the steps in photosynthesis are very rapid; many compounds may be formed in a few seconds. Through the use of radioactive isotopes, as illustrated in Figure 24, these dynamic life processes were unraveled. The successful discovery of the intermediate steps in photosynthesis was reported to the American Association for the Advancement of Science at the close of 1954.

ANIMAL STUDIES

Tracer studies in animal nutrition and animal physiology are similar in many ways to those in plant physiology. They cover a wide variety of interest. The problems and approaches are, also, very similar to those involved in the extensive use of isotopes in the studies of human physiology and metabolism. As a matter of fact, animal studies must often serve as a basis for application to human beings. A major portion of the radioisotope applications in the

animal husbandry field have been concerned with metabolism studies in poultry, cattle, and sheep.

Micronutrients

Radioisotopes are uniquely valuable for studying mineral metabolism, especially the extremely minute quantities of certain essential elements called micronutrients. Perhaps the best known and most striking of such studies is concerned with cobalt metabolism in the ruminant. Cattle and sheep require between 0.04 and 0.07 parts per million of cobalt in their diet, whereas simple-stomached animals such as horses, hogs, and rabbits have much lower requirements. Chemical studies of such low concentrations are extremely difficult. However, the problem easily lends itself to the tracer technique, which also permits the investigator to follow the metabolic path of the element.

Vitamin B–12 is known to be essential in minute quantities. Since the vitamin B–12 molecule contains cobalt, it was suspected rather early that cobalt deficiency in cattle and sheep was actually a B–12 deficiency. By oral administration of radiocobalt it has been confirmed that vitamin B–12 is synthesized in the rumen of cows and sheep and that oral administration is the most effective way to provide cobalt to animals deficient in this mineral.

Prior to work with radiomolybdenum, it had been assumed that molybdenum was essential for plants but not for animals. In recent work in Tennessee, radiomolybdenum was given to dairy cows. One of the important body enzymes, with radioactive molybdenum incorporated into the molecule, was then isolated from milk, showing that molybdenum is a part of this important enzyme.

Recent research with Sulfur 35 has shown that the amino acids, cystine and methionine, are synthesized by sheep and cattle from radioactive inorganic sulfate administered orally. In a rather surprising development, it was shown that the chicken also could synthesize the amino acid, cystine, from inorganic sulfate. Since cystine can partially replace methionine in the diet, inorganic sulfate may be considered an important and cheap nutritional mineral even for nonruminants.

Radioactive sulfur is being used in Wyoming to study selenium poisoning, an extremely important problem since many areas in western states are unused because of high selenium content in the soil. Selenium is taken up by plants and, when consumed by animals, has many toxic effects. Sulfur metabolism was shown to be affected by the ingestion of selenium. The latter is believed to interchange with sulfur in important amino acids, thus making them unavailable to the body. Through such studies a better insight is being gained on the mode of action of selenium.

Other studies include the use of radiophosphorus to investigate the metabolic relation of phosphorus with iron, cobalt, copper, and molybdenum in larger animals. Mineral metabolism in animals such as rabbits, chickens, swine, and cattle has been studied with the following radioisotopes: Cesium 134, Phosphorus 32, Sulfur 35, Calcium 45, Iron 55, Cobalt 60, Copper 64, Zinc 65, Strontium 89, Molybdenum 99, Iodine 131, and Tantalum 182.

Use of Organic Metabolites

Radioisotopes have found such extensive use in investigating organic and biochemical processes in animals, as shown by the large number of papers listed in Appendix V, that only a few of the noteworthy applications will be briefly discussed.

In several Southern states many better breeds of cattle do not thrive well because they are unable to adapt to high temperature and humidity. Several groups have conducted experiments in which animals with high heat tolerance, such as the Sindhi and Brahman, are crossed with other breeds in an attempt to develop animals with both heat resistance and high productivity. Prior to the use of radioisotopes, it was difficult to evaluate the ability of an animal to withstand high environmental temperatures. The more heat-resistant animals are believed to adapt themselves to high temperatures, at least in part, by a depression in activity of the thyroid gland.

Scientists in Missouri have injected radioactive iodine into animals exposed to various

temperatures and then measured the uptake of iodine by the thyroid with a counter. These studies are leading to a better understanding of thyroid depression and heat resistance, and are helping to identify animals with more than average heat resistance. The selected animals are used in breeding more heat-resistant cattle. Efforts are also being made to use similar techniques for prediction of performance potential in the young animal.

In the above section on micronutrients, the synthesis of amino acids from tagged inorganic sulfate was discussed. These same observations suggested that only the growing feathers of chickens take up methionine and cystine and that there is no exchange of these amino acids in the feathers with those in the body. The work also demonstrated that growth takes place only from the base of the feather. The growth of wool and the growth of feathers have much in common, so that radioactive sulfur also offers excellent opportunities for the study of wool growth and the effect of nutrition upon the growth of wool fiber.

By injecting cows with substances containing radioactive carbon and then measuring the radioactivity of expired carbon dioxide and various milk substances, investigators can establish the rate at which organic metabolites are broken down within the body and the extent to which the carbon in them contributes to formation of milk substances. The sensitivity of Carbon 14 as a tracer is illustrated in Figure 25.

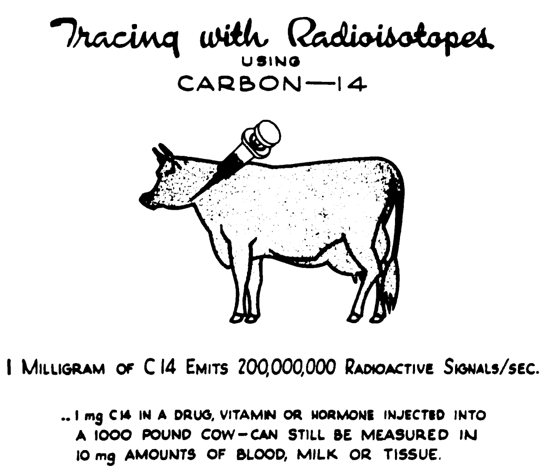


FIGURE 25.

Physiological Availability of Diet Additives

Radioactive tracers are used in a wide variety of ways to study the physiological availability of diet additives. Prior to the advent of radioisotopes for following complicated body processes, very little information on this important aspect of animal nutrition was known.

Conventional food balance studies give information only on intake and loss of nutrients from the body. Although excreta from animals contain materials that have not been absorbed, they also contain material which have been absorbed from the alimentary tract and subsequently excreted. This fact long interfered with estimation of the true digestion coefficient for feed materials, until the introduction of radioisotopes permitted identification of the source of excreted elements. Such uncertainty about mineral absorption is in contrast to organic nutrients, since the digestibility of these can usually be measured with accuracy by analysis of feed and feces. When organic nutrients are absorbed into the body from the digestive tract, they are broken down and not reexcreted intact into the gut. Tennessee and California scientists have succeeded in making definite separations of endogenous (body) and exogenous (feed) calcium and phosphorus in the feces. Similar studies have been extended to the egg, the fetus, and milk, making possible a clearer understanding of the relative contribution of the feed and body to each of these. This type of study is leading to a clearer understanding of the important processes of nutrition.

It has been long thought that the digestibility of the phosphorus of alfalfa hay for lambs was low, about 20 percent. This supposition is contradicted by recent studies made in California. The radioisotope tracer technique showed the true figure to be about 90 percent. Thus, alfalfa was proved an excellent source of phosphorus for the feeding of ruminants.

These procedures have emphasized the dynamic equilibrium of all elements within the animal body, and have made possible a new approach to determining body requirements of farm animals based on true digestibility of feed nutrients.

Biochemistry of Body Processes

For investigating the biochemistry of body processes, radioisotopes provide tools with practically unlimited possibilities. The work accomplished in this field on both laboratory and experimental animals is quite extensive, as indicated by Appendix V. (See secs. J and K.)

A great deal of research has been carried out with the dairy cow because of its importance as a provider of food. Much of this research has been done with the object of evaluating feed in relation to milk formation.

In the rumen of the cow, carbohydrates in the form of both starch and cellulose as well as proteins are acted upon by microorganisms and are broken down into small molecules. Radioisotopes show the principal end products to be acetic acid, propionic acid, and butyric acid. These are absorbed in the body for metabolic processes. Acetic acid is built into the body fats and other substances, used for energy, and converted into milk fats. Propionic acid is converted into liver glycogen, and butyric acid appears to be converted primarily into beta-hydroxybutyric acid. Knowledge of such processes is extremely important in improving milk production.

When acetic, propionic, and butyric acids containing radioactive carbon were injected into cows, it was noted that 17 percent of the radioactivity from the acetic acid, 11 percent from propionic acid, and 6 percent from butyric acid appeared in the milk, thus giving their efficiency of transformation into milk. When glucose containing radioactive carbon was injected into the cow, 56 percent of the radioactive carbon appeared in the milk. By analyzing the milk and studying the amount of activity found in each milk component it was shown which milk substances arise from acetic acid, propionic acid, glucose, and butyric acid. Such studies also suggest pathways by which biochemical transformations take place.

In a similar study, illustrated in Figure 26, radioactive glucose pumped through an udder by an artificial heart-lung apparatus has shown that all of the activity goes into milk sugar and practically none to other milk components. These studies show that glucose, when injected into the cow, is converted into substances such as fat and protein, which then are carried to the udder by blood and converted into milk

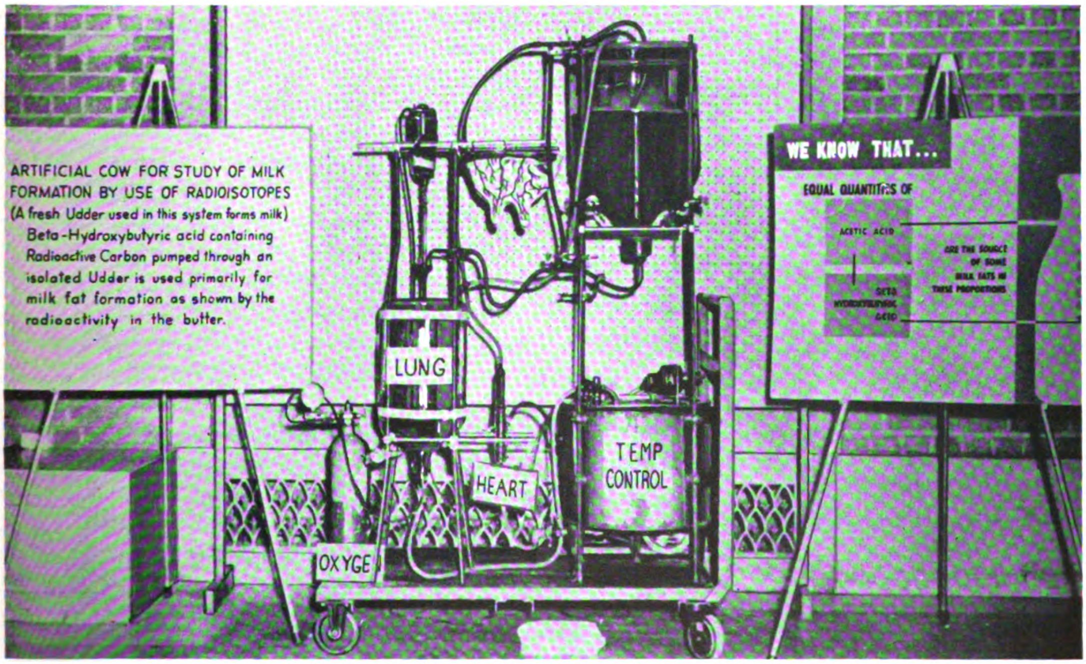


FIGURE 26.

components. A considerable amount of the glucose also passes directly to the udder and is converted into milk sugar. By the use of an artificial cow and radioactive glucose it has been possible to show that the udder itself utilizes glucose for milk sugar production only.

Information on milk forming reactions is showing the way to improved milk production in individual animals, the choice of economic feeds, better management practices, and choice of better stock for breeding.

Animal Diseases

Economic considerations often operate against using domestic animals to study diseases which affect them. Large domestic animals must be given si eable quantities of radioisotipes for investigational purposes, and their use creates special radiological safety problems. Results of work with small animals, such as rats, often can be extrapolated to larger animals.

However, certain specific problems must be investigated in the particular animal of interest. In many such studies, radioisotopes provide the best or perhaps the only approach to the problem. The following examples illustrate some of the applications.

In Maryland, radioisotopes have been used in work on ketosis in dairy cattle. Ketosis is caused by a hormonal deficiency that brings on a breakdown in the body's system of normal checks and balances. It has been shown that the hormone ACTH can be effective in its treatment. In other studies on bloat in sheep and cattle, a condition that results in losses amounting to millions of dollars, the use of radioisotopes is being planned as the most direct and profitable approach to a solution.

Strontium 90 beta-ray applicators have been used for treating infections of the eyes and skin in farm animals. Valuable breeding bulls with eye cancer have had their usefulness prolonged.

Chromium 51 and Phosphorus 32 have been used in labeling the virus which causes erythrogranuloblastic leucosis of fowls, and also a low-virulent strain of Newcastle disease virus of fowls. Cases of neural lymphomatosis and visceral lymphomatosis in fowls have been treated with Phosphorus 32.

Radiation Effects, Reproduction, and Genetics

Radioisotopes have been used extensively in specialized studies of experimentally produced radiation sickness in animals. Perhaps the most noteworthy are the studies of response of farm animals to radiation in which normal animals were subjected to lethal and sublethal amounts of radiation from Cobalt 60. Such studies have provided vital information on survival rates, physiology and pathology of irradiation, ability to perform work, and food potential of various farm animals in case of atomic disaster.

In other studies, uptake and retention of fission products in farm animals has provided useful information on the extent of radiation damage caused by these materials.

Radioisotopes are used in investigating important problems of placental transfer and deposition of elements in the developing fetus. These studies were peformed on cattle because their body size allows more detailed study of skeletal deposition and placental permeability.

The principles of genetics are believed to be universal from bacteria to man. Extensive studies of the genetic effect of radiation are being made with laboratory animals such as mice. Information gained in these studies will provide data necessary for an attempt to produce beneficial mutations in animals. Animal scientists hope that such mutations will result in increased economy in nutrition and in resistance to disease. Poultry raisers are using radiation in an attempt to produce genetic changes leading to increased egg production.

INSECT STUDIES

The number of species of insects and related arthropods are known to approach one million. The destructive and beneficial activities of these small creatures often determine the economic and social level of man's existence. Destruction of crops by the corn borer and several species of grasshoppers is an annual problem. Mosquitoes, house flies, and other insects spread both human and animal disease.

In the United States alone, it has been estimated that insects cause damage of over 3 billion dollars annually. Methods of controlling destructive insects generally depend on knowledge of the life history of the pest, to find a susceptible stage in the life cycle of the insect which can be attacked with an appropriate control method. Radioisotopes are helping in the search for better methods of controlling these destructive insects.

Despite the destruction and annoyance caused by most insects, many are useful. The perpetuation of many plants results through fertilization by insects. In addition to the honey bee, the silkworm, and lac insects, useful insects include predators and parasites which affect the balance of nature in a usually unnoticed fashion. Insects are useful also as experimental animals because of their small size, low cost of rearing and maintenance, and high rate of reproduction.

Sterilization

Scientists have utilized gamma rays from radioisotopes to interfere with the reproduction cycles of certain insects. The method is based on sterilizing large populations of male insects and releasing them with the knowledge that the female mates only once a year and with a single male. The resulting eggs will not hatch, thereby reducing the population in the next generation. U. S. Department of Agriculture scientists, working with Dutch authorities on the Caribbean island of Curacao, have been able by such methods to nearly eliminate screw worm flies, whose maggots attack livestock. Similar action in the United States has proved very effective. Losses to United States cattlemen from this pest are reported to total 25 to 35 million dollars per year.

The sterilization technique is useful only for the control of insects with suitable mating habits, and cannot be applied to a number of insect species.

In another type of study, scientists are devising ways for combatting the pink bollworm, which in 1953 accounted for a $261,000,000 loss to the United States cotton crop. Equipment utilizing radioisotopes as sources of radiation is being developed to kill the pink bollworm in cotton seed when it is removed from the fiber at the cotton gin. Ordinarily part of such seed is used by growers for planting the following year's crop. Thus, if the pink bollworm, which thrives in both the seed and the plant, is carted back to the field for planting it can continue its damage to a new crop. Sources for such radiation units may be obtained from waste fission product materials.

Insecticides

The use of radioactive insecticides has been a rewarding approach to the study of absorption and distribution of the toxicants in insecticides, particularly the ones that are systemically taken into plants. Information is obtained on extent of coverage during application, duration, systemic action within the plant, uptake by the insect, physiology within the insect, and other factors. Carbon 14 in various organic compounds has been most widely used in such studies. Iodine 131, Sulfur 35, and other radioactive isotopes have been used to a lesser extent.

Comparing the amount of insecticide absorbed by resistant and nonresistant strains of insects has helped to explain causes of resistance. Tracer studies in Oregon showed that a particular type of mosquito larva with acquired resistance absorbed over six times as much DDT as the same variety with no acquired resistance. Mortality of resistant larvae was 74 percent and of nonresistant larvae was 94 percent.

Some of the most important insecticides are also toxic to mammals. Sulfur 35-labeled parathion has been used to study the toxicity of this insecticide in rabbits. Phosphorus 32 has been used in the study of parathion in cows and milking goats.

In Iowa, work has been done on measurement of wireworm reactions to soil insecticides by tagging the insects with radioactive cobalt. The technique has several unique and important applications to the study of soil-infesting insect pests, and perhaps to other destructive insects such as stored grain pests which cannot otherwise be traced in their movements without disturbing them.

Migration and Hibernation

The use of radioactive isotopes to tag insects for flight-range measurements has been most helpful in the study of their habits of migration and hibernation. Phosphorus 32 and Strontium 89 are the radioisotopes most frequently used. Study of the ratio of tagged to untagged recaptured mosquitoes gives valuable clues to the productivity of breeding areas, and thereby aids in control activities.

Flies play an important part in the dissemination of dysentery and typhoid, and possibly poliomyelitis. Information of fly movements is essential, therefore, in planning field control operations. Fluorescent dyes, colored dusts, and chemical agents producing color reactions have been used in marking adult flies for dispersion studies. Certain mutant strains have been employed in special cases. These methods require the inspection of individual insects. The radioactive tracer technique has proved to be a far more versatile, quick, and accurate method for conducting these studies.

Such studies established that the major portion of house fly dispersion in a community falls within 1 mile of the release point, although movement can and does occur up to distances of 2 to 7 miles.

Radioisotope tracer studies also showed that blow flies disperse more rapidly and to greater distances than the house fly. Since blow flies frequent both disease sources and human foods and are a proven carrier of disease, their extended dispersal range increases their potential health hazard.

Cockroaches sprayed with radiophosphorus have demonstrated how the species can invade homes, even passing through water traps in the plumbing. Sewer cockroaches were used in one such experiment. The results showed that the insects, which are potential disease carriers, migrate as much as 200 feet when they become overcrowded or when forced out of their colonies by backed-up sewage.

Bee Culture

In bee culture studies in Wyoming, radioisotopes are being used to follow the spread of honey bee diseases by carriers between colonies. Phosphorus 32 was fed in sugar syrup to a colony of honey bees located in the middle of a row of colonies in an apiary. The drifting of bees from the marked colony to another colony was observed in relation to the spread of one of the brood diseases of bees, known as foulbrood. The drifting of tagged bees from the colony that had consumed some of the radioactive sugar syrup was easily followed by using a geiger survey instrument in examining the other colonies. Radioactive phosphorus is also being used in Louisiana to follow the feeding habits of bees.

Physical and Chemical Research

It was through the efforts of physicists and chemists that isotopes were discovered and ultimately produced in useful quantities. These scientists soon found isotopes to be very important tools in many of their fundamental research problems. As tracers for physical and chemical processes involving individual atoms and molecules, isotopes have no equal.

Isotopes represent one of the great extensions in man's ability to "see" and to "sort." At first, things could be seen only with unaided eyes and sorted out only with hands. Next, magnifying glasses and small tweezers were used. Later, the microscope was invented to see finer details and chemical and physical processes were developed to sort out various elements, compounds, and forms of life. As an "atomic" microscope, isotopes now take man another great stride forward in perception.

Both radioactive and stable isotopes are widely used in physics and chemistry. The statistical data on shipments of the two kinds, given in tables 1 and 4 of Appendix III, do not adequately reflect the importance of stable isotopes. Unlike the radioactive ones, which must be used while still "hot" and, in most instances, be replaced each time they are used, the stable variety do not change with time. Once obtained, they can be used over and over, as long as they are not too diluted with other isotopes of their chemical element during the experimental procedures.

PHYSICS

Nuclear physicists, in particular, have benefited by ready availability of a large variety of stable and radioactive isotopes. Even though particle accelerators and neutron sources allow the physicist to produce his own radioisotopes, a handy catalog of ready-made ones is extremely valuable. As byproducts of nuclear reactor operation they are available in quantities far larger than could be produced in a cyclotron.

Concentrated stable isotopes have been even more useful in nuclear research than the radioactive species. They are particularly useful as "purified" nuclear species with which to perform nuclear reactions, and to determine spin, magnetic moment, and other nuclear properties of interest to the physicist.

Stable isotopes have been of great help in the discovery and identification of new radioisotopes. Radioisotopes are discovered by finding a new half-life and energy of radiation and then obtaining conclusive evidence that the radiation comes from a particular isotope of a particular element. In most cases, a stable atomic nucleus hit by a nuclear particle is converted to a radioisotope of either the same element or one of its very near neighbors on the Periodic Chart. Chemical analysis of the target material then reveals which element is radioactive, but not which isotope of that element. However, if the physicist uses a single or concentrated isotope to start with, he can usually determine which isotope was formed from it.

The bombarding particle most often used in cyclotron reactions is the stable deuteron, the nucleus of double-weight hydrogen, or deuterium. It is obtainable, through the isotopes distribution program, as a gas or as heavy water, deuterium oxide. The radioactive nucleus of triple-weight hydrogen, or tritium, is also obtainable and used as a bombarding particle. Alpha particles are obtained as the nuclei of helium atoms, while Helium 3 particles are obtained from the decay of tritium.

Concentrated stable isotopes are frequently used as target material for the production of relatively pure radioisotopes in a nuclear reactor. Neutron irradiation of natural iron, for example, produces about equal activities of Iron 55 and Iron 59. Either of these can be obtained almost free of the other by irradiating iron enriched in Iron 54 or Iron 58, respectively.

Peculiar characteristics are found among the hundreds of stable isotopes and some of these have proved particularly valuable in pure form. Boron 10, for example, has an especially high probability of capturing a slow neutron. When capture occurs, B–10 converts into an alpha

particle and a lithium nucleus, both with high velocity. This special property makes B–10 useful for measuring or counting neutrons. Slow neutrons usually pass through a geiger counter without being counted, but a coating of Boron 10 in the counter absorbs a large proportion of them. The resulting particles from the B–10 trip the counter.

Concentrated stable isotopes have also proved useful in fundamental studies of the energy states, or levels, of atoms and molecules. These particles, when excited, emit visible light, infrared and ultraviolet light, microwaves, or X-rays. All are the same kind of radiation, but differ in energy range. These radiations are the energy released when the energy content of an atom or molecule shifts to a lower, more stable level. The spectroscopist can determine the energy states from the emitted spectrum.

Formerly, much of this work was indefinite because the weight of an atom affects its internal energy to a small extent and quite decidedly affects its vibrational energy in a molecule. In ordinary mercury, for example, seven different weights of atoms are always present and give slightly different spectra which blur together. By using mercury in which the isotope Hg–202 has been electromagnetically enriched from its natural relative abundance of 30 percent to 98 percent or better, the results become overwhelmingly those from one kind of atom and are quite definite.

The wavelength of the red line in the spectrum of cadmium was long ago set as the international standard of length. Although quite precise for most purposes, this standard suffers in being a combination of slightly different lines from the cadmium isotopes. Therefore, for still greater precision in laboratory wavelength comparisons, separated isotopes such as Cadmium 114, Copper 63, and Mercury 198 and 202 are used as spectrographic sources. Because mercury is so easily used in a light source, its enriched form as a practically pure isotope has been under consideration for possible replacement of cadmium as a primary standard.

Electromagnetically separated isotopes have been frequently used in search for natural radioactivity among the supposedly stable isotopes. When natural beta radiation from indium was confirmed, for example, a sample enriched at Oak Ridge to 99.92 percent Indium 115 was found to have more activity than normal indium, thus definitely pointing to Indium 115 as the radioactive isotope.

The physicist, also, sometimes employs radioisotopes as tracer atoms. Thicknesses down to a trillionth of an inch are measured in a method for calibrating the shadow-casting technique. Specimens to be viewed in an electron microscope are frequently sprayed at an angle with chromium or other heavy metal atoms so that "shadows" are formed which reveal varying depths of the surface. Atoms are evaporated in vacuum from a heated metal, as indicated in Figure 27. The resulting film must be thick

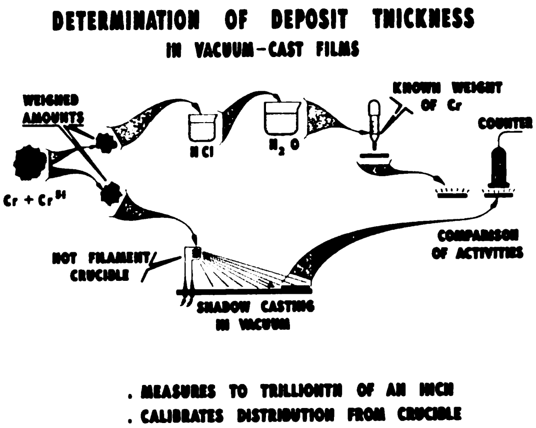


FIGURE 27.

enough to produce good shadows but not so thick as to blur details of the specimen. Thickness of film laid down in a given time at a particular place is determined by a test run with radioactive metal. A standard area of this film is measured for radioactivity with a counter. Solutions containing known weights of the same labeled starting material are dried on identical areas and are counted. Comparison of activities then gives the weight of film, for conversion to film thickness.

GENERAL CHEMISTRY

The chemist plays a universal role in technical endeavor. His investigations into fundamental chemical phenomena such as those discussed here form the basis for further progress in such diverse fields as medicine, biology, agri-

culture, and industry. The cause and cure of disease, the action of drugs, the mode of action of fertilizer and insecticides, the study of cell biochemistry, and a host of industrial processes, all require fundamental knowledge provided by the chemist.

Chemistry not only serves as the basis for a number of the unique techniques associated with the tracer method but also as the means by which tracer products are separated and identified. Indeed, the isotope tracer method depends very largely on chemistry.

The isotope tracer technique derives its power from its great sensitivity and specificity. Sensitivity is primarily concerned with the detection and measurement of radioactivity and hence is not the primary responsibility of the chemist. Specificity, on the other hand, depends on careful separation and identification procedures, which are chemical techniques. Further, the final radioactivity measurements in a tracer experiment are only as significant as the preciseness of the techniques used to separate and identify the samples.

The chemist has had to devise new methods and adapt others to meet these strict separation and identification prerequisites. Those most frequently used include ion exchange, chromatographic, and isotope derivative techniques. A brief discussion of these techniques will illustrate their versatility.

Separation of ionized substances by ion exchange is probably the most adaptable method at very low concentrations. Ion exchangers are substances which are insoluble in solvents and aqueous solutions usually employed in the laboratory, but which ionize in certain solvents. Under proper chemical conditions, the "charged" exchanger is extremely selective in reacting with ionized substances in solution. After being selectively absorbed, the separated substance (isotope) may be removed from the ion exchanger. This is one of the few methods of separation which operates more efficiently when substances are present at very low concentrations than when they are present in appreciable amounts.

Paper chromatography has proved a particularly useful technique since it permits separation and identification to be made in the same operation. Movement of a solvent along a strip of paper causes certain molecules to move with it, usually at a slower rate. Different compounds (molecules) move at different rates, thus permitting separation of mixtures of compounds in the chromatogram. Identification of the separated compounds may then be made by comparison with known chromatograms or by a combination of radiochemical and microchemical techniques. Two-dimensional paper chromatography has been introduced into isotope work and offers the advantage of a second order of separation. After one solvent has caused the products of an unknown mixture to move along one dimension of the paper, the chromatogram is rotated 90 degrees and a second solvent is added so that the partially separated products move in a second path at a right angle to the path of the original separation. Autoradiography has been found to be a helpful adjunct to paper chromatography.

The isotope derivative method, like paper chromatography, finds widest application in biological tracer studies. Briefly, it is a method for determining organic compounds from their isotopically labeled derivatives. To a mixture containing the compounds to be analyzed is added an isotopically labeled reagent under such conditions that the compound in question is converted into a derivative of the reagent. The isotope derivative method becomes quantitative (1) when quantitative yields are obtained of the isotopic derivatives during the reaction with the isotopic reagent as well as in subsequent isolations or (2) when a known amount of the compound being determined is labeled with a second isotope and introduced into the mixture. The recovery of the second isotope in any pure isolated sample of the isotopic derivative may be used to correct both the lack of quantitative yield and recovery obtained with the derivative of the original isotopic mixture.

For example, to determine glutamic acid in an amino acid mixture, one reacts the mixture with a certain radioiodine-labeled reagent, adds a known amount of very pure radiosulfur-labeled glutamic acid, and then separates the amino acids by chromatography. If the ratio of counts of radioiodine to radiosulfur is determined in successive small strips over the glutamic acid band, one can identify with

certainty and measure the amount of glutamic acid in the original mixture.

Throughout the course of all tracer experiments the isotope user must be continually aware of pitfalls. Potential pitfalls lie in each of the seven criteria of tracer methodology, namely: radiochemical purity, single chemical state, exchange error, degree to which the tagged molecule remains intact, isotope effect, chemical effects, and radiation effects. It is primarily the responsibility of the chemist to see that such pitfalls do not invalidate the results of tracer experiments.

PHYSICAL CHEMISTRY

Atom Exchange

Exchange of like atoms, between two different chemical species in solution, occurs spontaneously and can be detected and measured only with isotopic tracers. It occurs, for example, in a solution containing two types of complex cyanide molecules, each having an iron atom. The iron atoms exchange position between the dissimilar molecules, while the number of molecules in each species remains unchanged.

After labeling one species with radioiron and allowing exchange to occur with the other species over a definite period of time, the two are chemically separated and the radioactivity is measured in the second species. Such observations on the rate of exchange can shed much light upon the strengths of various chemical bonds. Strong bonds would prevent substantial exchange.

Aging of Precipitates

Alteration of chemical precipitates with time has also been studied with radioactive tracers. When a solid is precipitated from solution there are always a definite number of molecules which remain dissolved, depending on the solubility of the precipitate. A newly formed precipitate differs in character from an "aged" precipitate and the solubility often varies with aging. Tracer studies have clearly demonstrated what was long suspected, namely, that the precipitate spontaneously redissolves and reprecipitates (recrystallizes) to form a new and more stable surface during aging. The use of radioisotopes to measure quantitatively the very small solubilities of many solids has proved valuable to analytical chemistry.

Surface Reactions

Surface phenomena involve special and complex mechanisms for which radioisotopes frequently provide the chemist his only method of study. Even as seemingly simple an action as corrosion is quite complex and much effort is being made to gain a better understanding of it. The "passivity" or inertness to corrosion which is induced in iron by treatment with chromate was studied, using Chromium 51-labeled chromate. An autoradiograph of the surface showed concentrations of the chromium at areas where early corrosion had been arrested. Various theories have been proposed to explain passivity and results of this test were useful in supporting one of the theories.

Radioisotopes are useful in studies of surface reactions frequently encountered in industrial processes. In studying reactions involving surfaces of solids, powders, or colloids, determination of the surface area is frequently important. No ordinary measuring technique reveals the surface of a powder but many methods have been devised for estimating these areas. The method using radioisotopes is generally in agreement with others and is usually faster and more convenient. It involves selective transfer (adsorption) of radioactive atoms from a solution onto the surface and determination of the area from the number of atoms on the surface.

Water flotation of mineral ores for separations in the mining industry is based on the adsorption of certain organic chemicals on the mineral particle surfaces. Since the chemicals coat one type of particle better than another, it is possible to make one kind float in a froth so that it can be skimmed off while the other sinks. By using a radioactively tagged chemical and a counter, it is possible to determine the conditions for and extent of adsorption on any particular mineral. The use of dodecyl amine for the flotation of quartz was studied in this way by using C-14-labeled amine. Economically important results were obtained on the fraction of surface which had to be covered to achieve

flotation and the grams per ton which gave optimum results.

Surface reactions are of great importance to the manufacturer and user of detergents and of laundry equipment. Adsorption on cloth fibers of both the soiling substances and minerals in hard water must be combatted by chemical action of the detergent. Many tracer techniques with radioisotopes have been devised for evaluating the efficiency of cleaning agents. In a typical test, swatches of cotton cloth were cleaned with various detergents in wash and rinse waters containing calcium bicarbonate labeled with radiocalcium. Little or no radioactivity remaining on the washed cloth indicated high efficiency in removing calcium ions absorbed on the surface.

The soiling substance also is frequently made radioactive for testing the efficiency of detergents or washing equipment and techniques. Fats, proteins, carbon, and clays have been labeled for this purpose. Automatic washing machines are routinely tested in this way by some firms.

Many important chemical reactions can only be made to proceed on a commercial scale by means of catalysts. Adsorption, reactions, and exchange on the catalyst surface are imporant factors in surface reactions. Information regarding these factors can be obtained with tracer isotopes and may be of vital importance to an industry. A tracer study of the Fischer-Tropsch synthesis of gasoline and other important hydrocarbons from hydrogen and carbon monoxide is an example of such work.

Diffusion

Isotopic tracers are particularly useful for identifying and following particular atoms or molecules in a chemical or physical system. In studies of gaseous, liquid, or solid self-diffusion there is virtually no other way to distinguish the diffusing atoms or molecules from chemically identical neighbors in the surrounding material. Such studies are not only of fundamental value in the understanding of molecular dynamics but are of potential use in many metallurgical and chemical processes.

A tracer study of solid metal self-diffusion, as affected by temperature, is illustrated in Figure 28. In the procedure, a thin layer of radioactive copper atoms is deposited on a copper block. The surface radioactivity is then found to decrease as surface atoms migrate into the block and the radioactive atoms among them are replaced by inactive ones. Self-diffusion in gases and liquids is usually studied by introducing the tracer at the end of a long, thin tube containing the material and measuring the radioactivity along the tube.

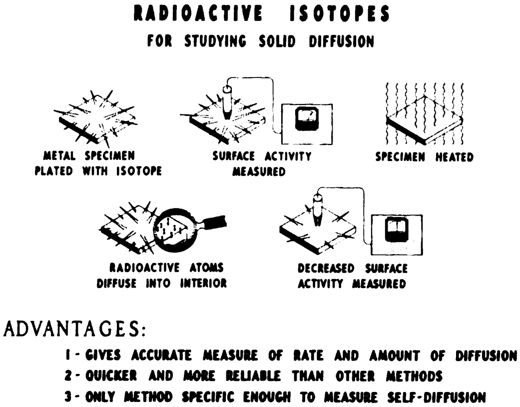


FIGURE 28.

Diffusion between dissimilar materials can be investigated in the same way. Such studies are particularly valuable in the case of metal alloys, where the strength and other characteristics depend on the distribution of the unlike atoms.

Vapor Pressure

The superior sensitivity of radioisotope measurement as an analytical method is shown in a method for measuring vapor pressure over solid or liquid metals. With metals of high melting point, it takes hours or days to collect enough condensed vapor to allow accurate weighing. By adding a radioactive tracer to the metal, as indicated in Figure 29, the determination may be made in a few minutes.

In a typical study, Silver 110 is added to melted silver. The vapor from the hot metal is allowed to stream through a pinhole in the crucible lid and condense on a cold metal disk. The activity collected in a certain time is measured with a geiger counter, and from it the amount of evaporated metal and the vapor pressure are calculated.

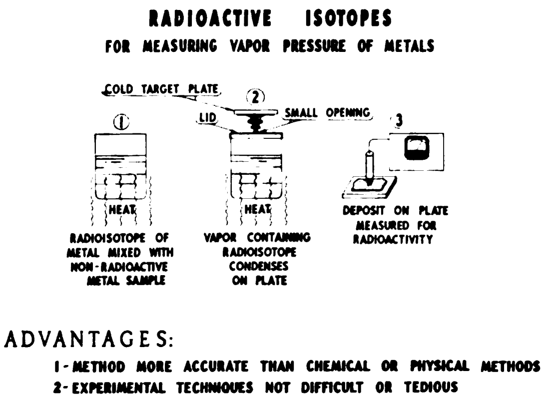


FIGURE 29.

Thermodynamic Properties

The great sensitivity obtainable in radioisotope tracing allows the chemist to use extremely small quantities of material when he finds this desirable. The thermodynamic properties of solutions, for example, are usually extrapolated to their values at "infinite dilution" since they change significantly with concentration. The researcher can verify or study thermodynamic behavior in a quantitative manner at extreme dilutions by using radioactive solutes.

Activation of Chemical Reactions

Radioisotopes are not only valuable in studying chemical reactions but also in causing them. Radiation is able to cause chemical changes by producing ionized molecules or free radicals (detached parts of molecules) which react in turn to form new molecules and, hence, new chemicals. Production of new or better products with radiation has great economic significance, and industrial potentialities are discussed in the section on Industrial Uses.

Chemical reactions best suited to activation by nuclear radiation are those which are "triggered" by penetrating particles, rather than those depending upon radiation energy to carry on the reaction. Chemical processes based on this type of action can be classed as polymerization, cross linking, halogenation, and oxidation.

Polymerization refers to chemical reactions in which many molecules are joined in a long chain as one large molecule called a polymer. Many important materials such as plastics and synthetic rubbers are produced in this way, entirely by chemical means. Rupturing of bonds to form new points of attachment for additions to the chains can also be effected by nuclear radiations. New materials may be produced in this way that are not possible or practical with present means. Reactions which have been studied include the formation of polymers of acrylates, styrene, and acrylonitrile.

The initiation of cross-linking of long-chain polymers is an effect of radiation receiving much attention in research. Molecules of a thermoplastic material such as polyethylene have many carbon-hydrogen bonds which can be broken by radiation. A single high-energy particle can produce this effect in thousands of molecules. The open bonds then join permanently to those of adjoining chains. Cross-linking prevents easy sliding of the molecules and thus changes the melting point, solubility, strength, and other characteristics of the material. Polyethylene, for example, melts to a thick liquid at about 70° C but retains its shape to 190° C after cross-linking.

Halogenation reactions, in which chlorine, iodine, and other halogens are joined to other chemicals to produce new compounds, are often extremely slow but can be greatly speeded up under ultraviolet light. The triggering energy can also be supplied by nuclear radiation. Oxidation reactions, also, make up a large group of chemical processes. Modern chemical theory assumes that in many oxidation reactions there is a chain reaction of free radicals in the presence of oxygen. Radiation is effective in producing free radicals as well as ions and may lead to easy oxidation of materials ordinarily difficult to oxidize by other means.

ORGANIC CHEMISTRY

The chemistry of carbon compounds, as this branch of science is usually described, has benefited greatly from the isotope-labeled organic compounds now available. The older literature in this field proposed many different mechanisms and theories for a single chemical reaction. With no way to trace individual carbon atoms, investigators were at a loss to resolve

the differences between various proposed mechanisms and theories. Carbon 14 has provided the key to understanding. Hundreds of compounds have been labeled with this isotope alone.

The Crossed Cannizaro reaction, for example, has been known for nearly 100 years. It involves a reaction between an aromatic aldehyde and formaldehyde. The formaldehyde is oxidized to formic acid and the aromatic aldehyde is reduced to a carbinol. To prepare a carbinol isotopically labeled in the carbinol carbon atom, one might consider starting with the corresponding aromatic aldehyde labeled with C–14 and performing a Crossed Cannizaro reaction with formaldehyde. An effort to do this came to nought, however, because all the radioactivity appeared in the formic acid, leaving a nonradioactive carbinol. Apparently, the formaldehyde carbon traded places with the C–14-labeled aldehyde group. Without the use of the radioisotope label, this mechanism would not have been discovered.

In studying chemical reactions, once the mechanism is known, the next stage is to determine the kinetics of the reaction. Prior to the use of isotopically labeled compounds it was not possible to study the kinetics of a reaction under equilibrium conditions. Data on the progress of a reaction had to be obtained by chemical analysis, requiring that a reaction proceed a substantial degree in one direction so that changes in concentration of reactants and products were great enough to be measured. Reaction rates so far from equilibrium, however, may not be the same at equilibrium. Isotopically labeled reactants allow kinetic studies under equilibrium conditions and provide the kineticist with an extremely sensitive means of measuring rates and determining the reversibility of a reaction step.

The Menschutkin reaction provides an illustration of the latter point. It involves the formation of a quaternary salt from an alkyl halide and a tertiary amine. A steric orientation in the collision of the reactant molecules was thought by many to be necessary to permit the formation of an activated intermediate complex which could then dissociate to form the products. Other workers postulated the *reversible* formation of an activated intermediate complex, that is, one which could disassociate to form either the original reactants or, under favorable circumstances, the products. To investigate this problem, a Menschutkin reaction was performed with an isotopically labeled alkyl halide. When the reaction was only partially complete, the other reactant, the tertiary amine, was assayed for radioactivity. None of the isotopically labeled alkyl groups appeared in it. If a reversible intermediate had been formed, however, in which the alkyl groups were spatially equivalent, labeled alkyl groups would have been found in the unreacted tertiary amine. This indicated either that the intermediate complex does not reform the reactants to an appreciable extent or that the alkyl groups are not spatially equivalent. Thus, through the use of radioisotopes, evidence was obtained which indicated that a reaction which was thought to be reversible actually proceeded only in one direction.

Although radioisotopes are extremely valuable in kinetics, their use interposes an additional factor, the isotope effect, in rate studies. This additional complication can be turned to advantage, however. Two factors are involved in changes in reaction rate resulting from isotopic substitution. One is the lower frequency of rupture of the critical bonds in the activated intermediate complex containing the heavier isotope. The other is the higher activation energy for dissociation of the heavier molecule. In hydrolysis of an ester, for example, substituting C–14 for C–12 in the carbonyl carbon caused the molecule to react somewhat more slowly. This indicated that the rate-determining step involved breaking a bond to the isotopic label.

The rate-determining step in the decarboxylation of an aliphatic acid could not be identified from available kinetic data. A study employing isotopic carbon, however, revealed a reaction rate difference due to the isotope effect, thus leading to the conclusion that the step in question was the breaking of a carbon-carbon bond.

Perhaps the most striking example of the chemist's important role can be found in his contributions to unraveling the complicated process of photosynthesis. Here we have one of the most complex of natural phenomena, where starting with carbon dioxide, water, and the

energy of the sun, plants synthesize the complicated compounds upon which human life depends. The chemist, with his knowledge and techniques, spearheaded research in this field. With his tracer methods he determined the different compounds which are produced, by isotope dilution analysis he measured the amounts of each, through mechanism studies he followed the synthetic pathways in the plant, and via kinetic studies he determined the reaction rates and the nature of the bonds involved in the various reactions. There was no phase of this problem which did not call upon the chemist's talent.

Industrial Uses

As the atomic energy program entered the year 1950 there were approximately 100 industrial firms exploring the uses of radioisotopes as new industrial tools. Today, nearly 1,200 industrial firms comprise almost 50 percent of all institutions using radioactive materials. This recent striking growth has seen the use of atomic energy, in the form of radioisotopes, pushed into most major industrial fields. These uses have created widespread interest among other firms which are hopeful that these same principles may be adapted to solve some of their own particular problems.

Employee training is still the biggest bottleneck in wider industrial use of atomic energy. However, a recent increase in number of training courses, as noted in the section on training, is rapidly improving this picture.

The recent years of radioisotope distribution have indeed witnessed a phenomenal growth in industrial uses. Industry is no longer reluctant to bring these valuable tools into its plants and laboratories.

The bibliography on applied industrial uses, in Appendix V, CC, lists more than 200 papers published within the past 3 years. Since industrial development usually involves "trade secrets" with patent potentialities and production advantages, this number of papers is noteworthy.

The nuclear principles involved in most industrial applications are not profound. As a matter of fact some of these uses were conceived toward the end of the last century when radium and X-rays were first discovered. These potential industrial uses spurred the early development of atomic energy and early uses of radiation.

Since there are hundreds of industrial uses of radioisotopes, the various applications are broken down here into several types of use and a few representative examples of each type are discussed.

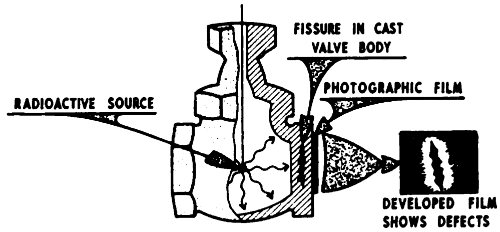
PENETRATION OF RADIATION

The ability of radiation to penetrate matter has led to the most extensive industrial use of radiosotopes. A part of the radiation is always stopped by the material being irradiated; the amount depends upon the type and energy of the radiation being used and upon the density and thickness of the material and any flaws which may be present.

Radiography

Industrial radiography is one of the large uses of radiosotopes. Its principle is illustrated in Figure 30. Radiography with radium, of course, is a comparatively old method for inspecting metal castings and welds for possible flaws not otherwise detectable. Reactor-produced Cobalt 60, Cesium 137, and Iridium 192 are now used in much the same way as radium but are much cheaper and more effective. Cobalt 60 equivalent in radiation intensity to $20,000 worth of radium can be purchased for about $100. The radiation from Co–60 will penetrate thicker sections of steel than will the rays from radium.

RADIOACTIVE COBALT – Co 60
FOR RADIOGRAPHY TESTING



ADVANTAGES:

1- VERSATILE AND RELIABLE INSPECTION
2- INSPECTION MADE WITHOUT DISMANTLING
3- SOURCES OF DESIRED SHAPE AND SIZE
4- VERY HIGH ACTIVITY SOURCES AVAILABLE AT LOW COST

FIGURE 30.

Thickness Gaging

In another application of the radiation penetration principle, the transmission-type thickness gage is being used routinely on production lines to help produce more uniform paper, aluminum, copper, tin plate, plastics, rubber, glass, and numerous other items. This continuous, noncontacting method of gaging is especially useful where products are moving rapidly, where temperatures are high, and where products are soft and may be easily marred. As illustrated in Figure 31, the material whose thickness is to be gaged is passed between a source of radiation and a radiation detector which is connected to an amplifier and recording device. In many cases, the signal caused by the radiation transmitted through the material is used to make automatic corrections in the production process.

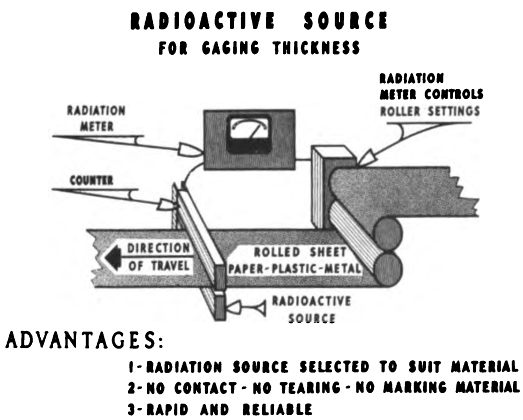


FIGURE 31.

Nuclear gages have taken many interesting and ingenious forms. To control ink distribution during lithographic printing, for example, a special built-in thickness gage was developed in which the inking rollers, themselves, serve as radiation sources. A small amount of the low-energy beta emitter Nickel 63 was electroplated on the rollers and "flashed" with a thin protective layer of copper. Detectors near the rollers recorded the beta particles penetrating the 4- to 6-micron thicknesses of ink. By this means, ink film thicknesses were determined on all rollers under dynamic conditions.

Density Gage

In the transmission type of thickness gage the amount of radiation picked up by the detector is, of course, dependent upon the amount of material between it and the radioactive source. In such thickness measurements it is assumed that the density of the material remains constant. Conversely, if the thickness or size of a material remains constant, the same gage may be used to measure density. Examples of such an application are the monitoring of the density of a process fluid flowing through a pipe or the moisture content of sand or other material.

A recent and interesting variation of the radioactive density gage is being used to determine the hydrogen-to-carbon ratio in an analysis of hydrocarbon compounds, including fuels. The principle, illustrated in Figure 32, involves the difference in beta-ray absorption caused by variations in electron density, this density in turn depending upon the hydrogen-to-carbon ratio. The commercially available device is expected to be particularly useful in conducting various fuel tests, but should have other applications as a quick check on the constitution of certain organic products.

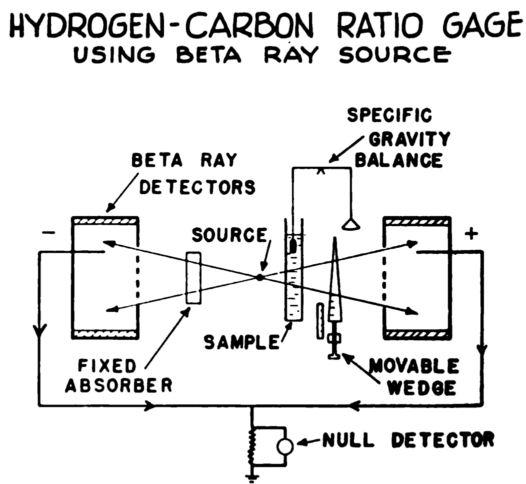
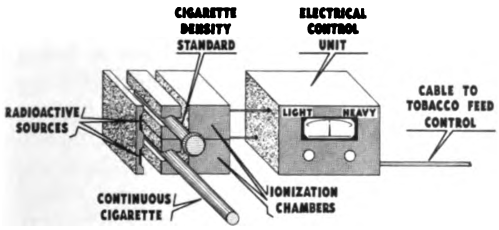


FIGURE 32.

An excellent example of how a radioisotope can be adapted to a high-speed packaging problem is illustrated by a recent development in the cigarette industry. Over the past years this industry has expended considerable effort

to improve production quality control with respect to cigarette weight. The average weight of a cigarette is an important factor in cigarette quality. A light-weight cigarette burns both fast and hot, whereas cigarettes that contain more tobacco than necessary are hard to draw through and are costly since tobacco represents about 90 percent of the production cost. A density gage, in Figure 33, using Strontium 90 as the source, permitted automatic adjustment of tobacco feed and contributed to uniformity of product.

GAUGING CIGARETTE FIRMNESS
WITH RADIOISOTOPES

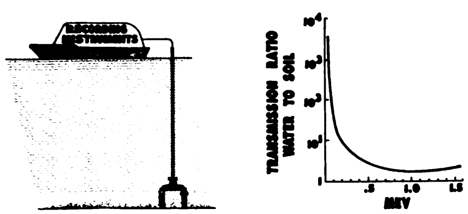


ADVANTAGES: 1-MORE UNIFORM FIRMNESS
2-SAVES TOBACCO
3-ELIMINATES MANUAL CONTROL

FIGURE 33.

Radioisotopes have been used to solve the problem of measuring silt at the bottom of large bodies of impounded water. As illustrated in Figure 34 a density gage was developed which utilizes low-energy bremsstrahlung radiation, the X-rays caused by beta ray emitters.

BREMSSTRAHLUNG GAUGE
FOR
MEASURING SILT DENSITY



ADVANTAGES: 1-MORE ACCURATE
2-MEASUREMENTS EASILY AND QUICKLY MADE
3-ELIMINATES COLLECTING SAMPLES

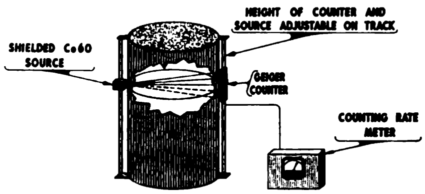
FIGURE 34.

With Strontium 90 in one side of a two-pronged device and a radiation detector in the other, changes in silt density between them affected the transmission of X-rays sufficiently for accurate measurement.

Liquid-Level Gage

The radioactive liquid-level gage is similarly based on measuring the change in intensity of a beam of radiation from a fixed source. As shown in Figure 35, the source is sometimes mounted on one side of the tank or vessel containing the liquid and the radiation detector on the other side. When the liquid rises

RADIOACTIVE COBALT – Co60
FOR INDICATING LIQUID HEIGHT



ADVANTAGES:
1-GAGE NOT AFFECTED BY CORROSION AND TEMPERATURE
2-CAN BE OPERATED BY NON-TECHNICAL PERSONNEL
3-ADAPTABLE TO AUTOMATIC RECORDING AND CONTROL OF LIQUID LEVEL

FIGURE 35.

to a certain level, it cuts off or reduces the beam. This particular adaptation has, for example, been found advantageous in measuring the height of molten metal in a cupola since problems of corrosion and heat damage can be eliminated.

REFLECTION OF RADIATION

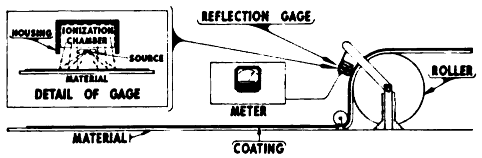
When a beam of radiation is directed toward a material, some of the radiation is reflected. The amount depends upon the type and energy of radiation and upon the composition, density, and thickness of the material.

Reflection Thickness Gage

Radiation reflection is serving a useful industrial purpose in the accurate measurement of thickness of coatings laid over a base metal. For example, it is possible to measure the thick-

ness of gold plated over copper or rubber over steel. The reflection-type thickness gage is illustrated in Figure 36.

RADIOACTIVE SOURCE
FOR REFLECTION (BACKSCATTERING) THICKNESS GAGE



ADVANTAGES:
1- CAN MEASURE THICKNESS OF COATING AND/OR MATERIAL
2- MEASUREMENT MADE FROM ONE ACCESSIBLE SIDE
3- CAN MEASURE A VARIETY OF MATERIALS WITH ONE CALIBRATION

FIGURE 36.

In this technique the beta particles, or electrons, from a radioisotope strike the base metal and the intensity of the reflected beam is measured. The metal is then coated with a different material (either metal or nonmetal), and the reflected radiation is again measured. The change in reflection is proportional to the thickness of the coating, up to a certain limiting value, and can be measured directly in microinches. Variations in coating thickness can be measured with good accuracy in most cases, and automatic adjustments can be made without stopping or cutting the sheet of moving stock.

The cost for the radioisotope included in such a gage is quite small, usually below $50. The associated electronic equipment is more expensive and may amount to several hundred dollars.

The applicability of the radioactive thickness gage is attested to by the number and variety of industries using them. A number of companies that started out initially with one gage in one plant now have many similar installations in other plants.

Soil Moisture and Density Gage

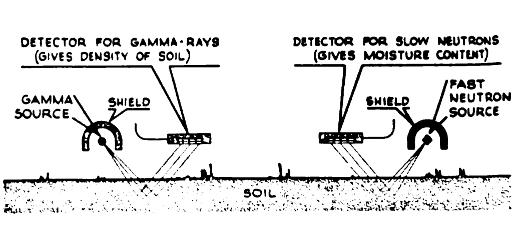
Soil-density and soil-moisture gages for use in the field are other industrial applications of the radiation reflection principle. These gages eliminate the delays incident to laboratory determinations. They have been used in the selection of suitable sites for aircraft runways, highway roadbeds, and hydroelectric dams.

Each apparatus uses a radioactive source, a radiation detector, and an electronic recorder. The source and detector are housed in a probe which can be lowered through a one-inch diameter steel tube driven into the ground. The soil density probe utilizes a Cobalt-60 source inserted in the tip of the probe. Gamma rays from the cobalt bombard the soil surrounding the tube and are scattered by it. Some return to the geiger counter which is mounted in the top of the probe and shielded against direct radiation from the Cobalt 60. The amount of reflected radiation can be translated directly into soil density in pounds per cubic foot.

The soil-moisture probe utilizes a neutron source activated either by alpha or gamma rays. Neutrons are strongly affected by the hydrogen atoms in soil moisture. When fast neutrons strike hydrogen atoms they are slowed down and after several such collisions some are reflected back to the vicinity of the probe. The top of the probe contains a geiger counter surrounded by a silver foil and shielded against direct radiation from the neutron source. When a reflected slow neutron strikes the foil, a short-lived radioisotope of silver is formed. The radiation from this rapidly decaying radioisotope is measured by the counter, which is insensitive to the neutrons themselves, and can be translated directly into moisture content of the soil.

The principle of the soil-density and moisture gage is illustrated in Figure 37.

Density and Moisture in Soil
AN INDUSTRIAL USE OF RADIOISOTOPES
IN ROAD BUILDING



1- DATA OBTAINED WITHOUT MOVING SOIL
2- GAMMA-RAY DETECTOR MEASURES DENSITY
3- SLOW NEUTRON DETECTOR SHOWS MOISTURE

FIGURE 37.

LUMINESCENCE

The ability of radiation to cause certain materials to emit light, or to luminesce, is a long-known and long-used principle. As a matter of fact, the science of radioactivity is a direct outgrowth of early interest in luminescence. Before the turn of the century, Jean Poincaré postulated an intimate connection between luminescence and the new X-rays found by Roentgen and the mysterious emanations from uranium found by Becquerel.

Luminescence is now a well-developed science with many promises for the future. Many special compounds emit a variety of light rays when struck by atomic particles. These self-luminous markers can be invaluable in emergency situations and have vitally important military applications. Routine applications include such uses as illuminating dials and clocks and providing photometric light standards.

A number of companies have investigated the possibility of using reactor-produced materials in place of naturally occurring radium and polonium in the manufacture of luminescent materials. Reactor-produced radioisotopes offers several advantages: first, pure beta-ray emitters reduce the health hazards involved; second, reactor-produced isotopes are usually easier to work with; and third, beta radiation has been found to cause less deterioration than the alpha particles of natural radioisotopes, leading to a more constant level of light output and longer life. Luminescence as an industrial use of radioisotopes is illustrated in Figure 38.

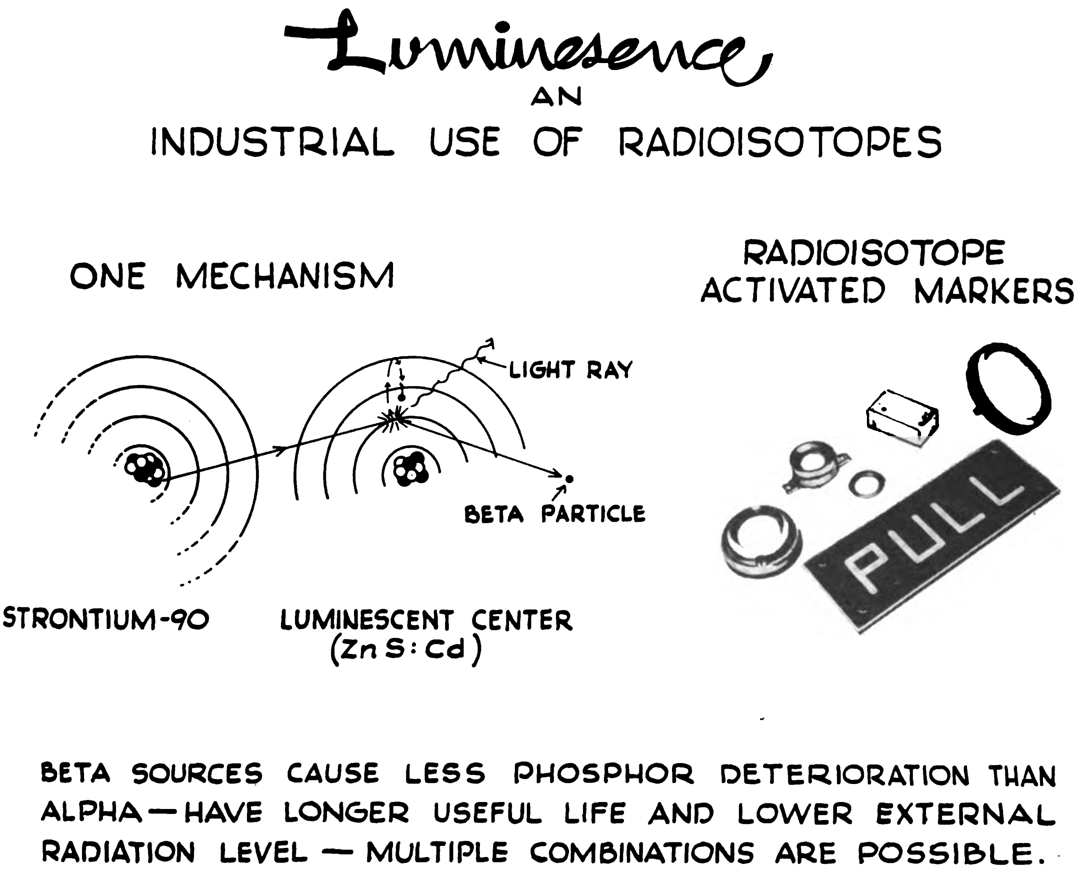


FIGURE 38.

IONIZATION

The ability of atomic radiation to ionize most of the materials it strikes can be put to many beneficial industrial uses. For example, static electricity in industry is a menacing problem to production and personnel and occurs quite generally whenever products manufactured possess insulating properties. Through their ability to ionize the air at selected points along the moving stock and thus "ground" the static electricity, radioisotopes help to meet this problem.

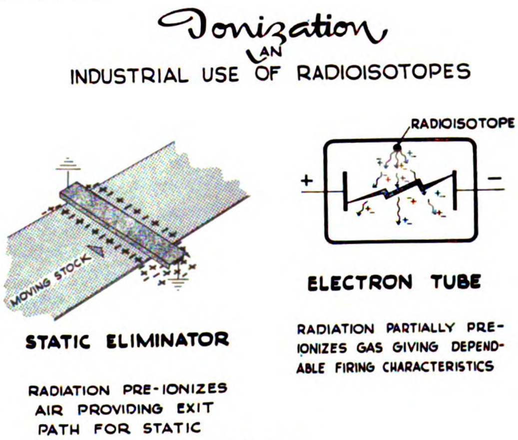


FIGURE 39.

The electron tube industry also is profiting from the ionizing ability of radioisotopes. A small amount of radioactivity inside certain specialized tubes keeps the gases in a partial state of ionization, allowing more dependable operation of the tubes. The use of radioisotopes as stabilizing agents for spark gaps in ignition systems is also being developed.

Ionization as an industrial use of radioisotopes is illustrated in Figure 39.

ACTIVATION OF CHEMICAL REACTIONS

Activation of chemical reactions is another industrial use of atomic energy that holds many possibilities. It has already been demonstrated that beneficial chemical and physical reactions may occur when certain materials are subjected to the proper amount of radiation. Many new compounds and, especially, some superior plastics have already been made in research operations.

The possibility of producing crosslinked, degraded, and formed materials under accurately controlled conditions by a purely physical process has valuable commercial possibilities. These will depend on the cost of irradiation, the enhanced value of the material, and the comparative cost of competitive chemical processes if they are available.

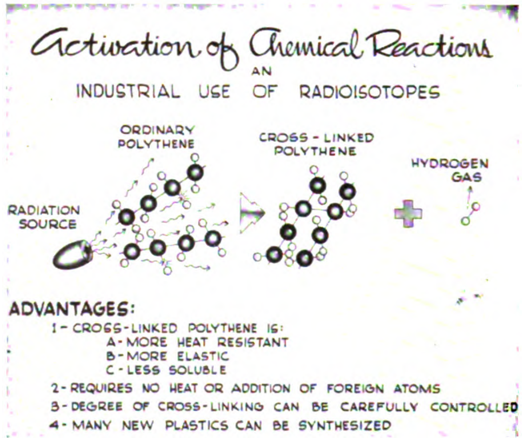


FIGURE 40.

As previously noted, irradiation increases the melting point of polyethylene from 70° to 190° centigrade. Irradiated polyethylene drug bottles and other containers can be sterilized without harm.

Activation of chemical reactions as an industrial use of radioisotopes is illustrated in Figure 40.

STERILIZATION

Gamma radiation in large enough doses can destroy bacteria and enzymes in a material without raising its temperature significantly. Many papers have been written since 1920 concerning the effects of ionizing radiation on all types of organisms. The recent availability of large sources of radiation from reactors has caused extensive interest in radiation sterilization.

The absence of high temperatures is quite necessary in the processing of many items such as antibiotics and certain other drugs. Large-scale sterilization or pasteurization of perishable food stuffs such as meats, bananas, potatoes,

and beverages holds interesting possibilities. Indeed, cold radiation sterilization has great potential importance.

The success of radiation sterilization and pasteurization will be determined by the enhanced value of products treated. If the irradiation process results in improved or longer lasting products, radiation treatment of many present day items should become profitable.

In the drug industry, radiation sterilization presents fewer problems. Side effects such as occur in many foods, are usually not important. It may be possible to utilize this type of sterilization in many pharmaceutical processes.

Radiation sterilization offers the first promising new principle of food sterilization since Nicholas Appert discovered the art of canning in 1809. Today, more than 40 institutions, including food industries, universities, research institutions, government laboratories, and the military, are actively engaged in radiation processing research. The activities of these many groups are being coordinated in the Quartermaster Food and Container Institute Radiation Sterilization Program. Many believe that this research will lead to the changing of food containers, preparation and processing methods, and distribution and marketing practices of food products.

Sterilization or pasteurization of foods by irradiation presents several problems as well as many promising aspects. Irradiation of some foods may cause changes in texture, color, taste, odor, or nutritional value. Intensive research is now being done to learn why unwanted changes occur and to devise ways to reduce or prevent them.

Irradiation of potatoes to delay sprouting and rotting is now being studied. Routine pasteurization of meats and beverages may be

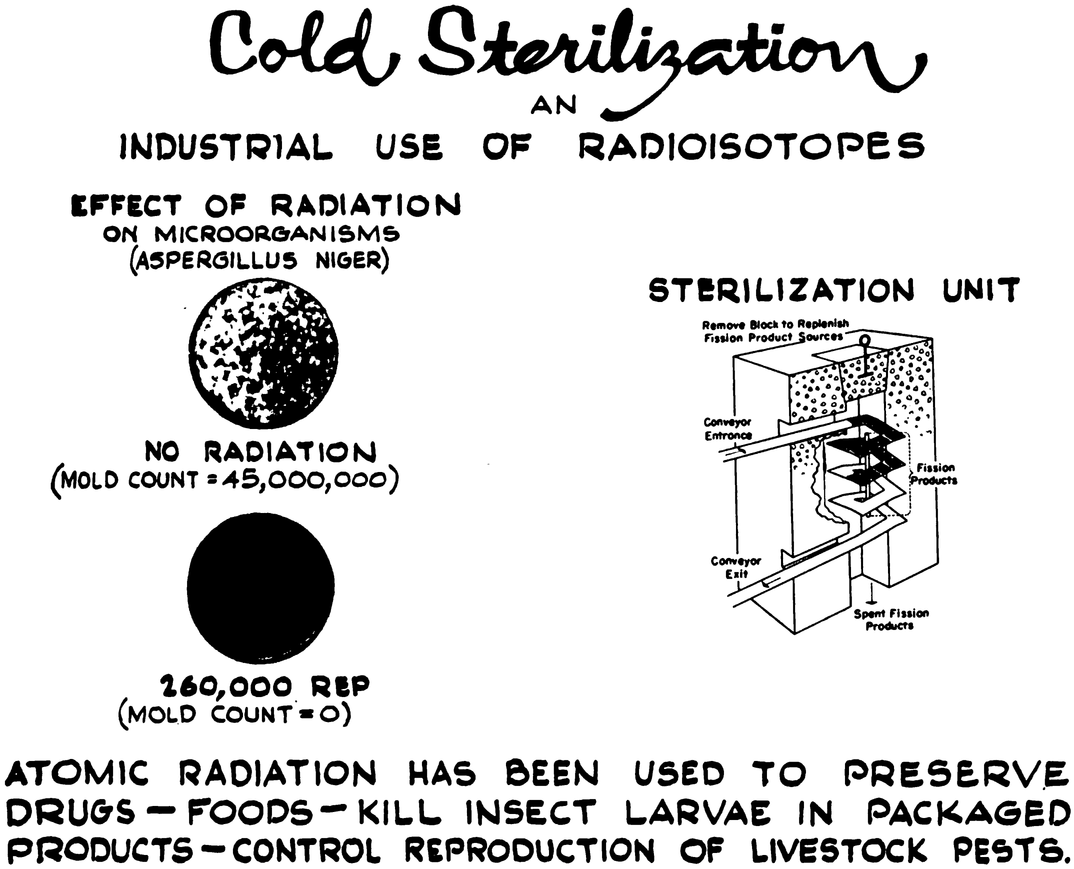


FIGURE 41.

IRRADIATION OF POTATOES IMPROVES STORAGE QUALITY

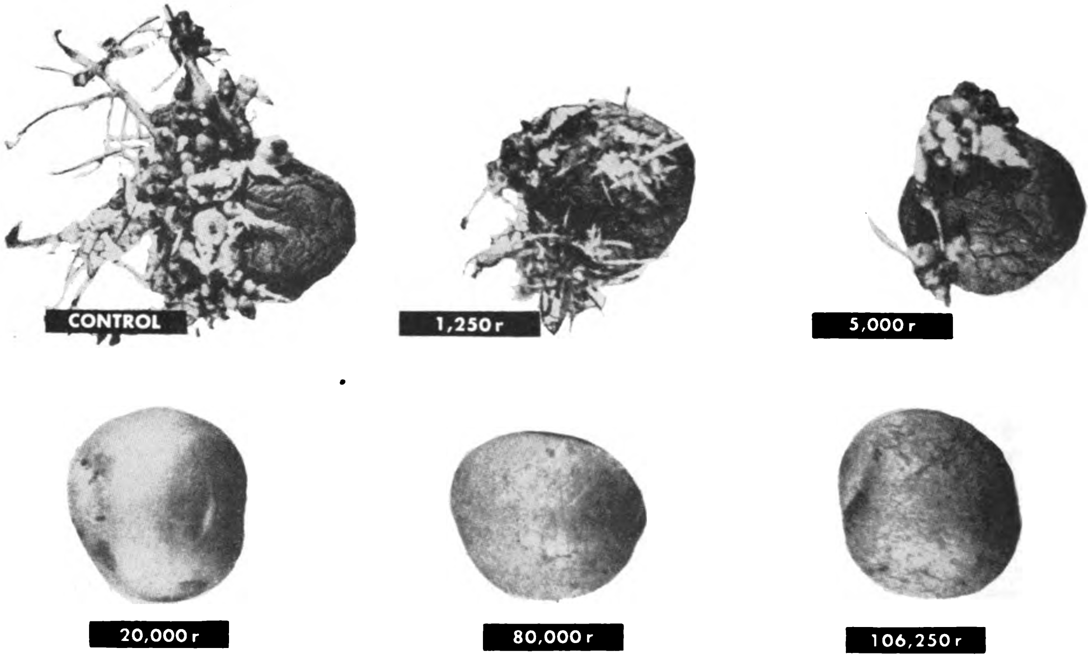


FIGURE 42.

feasible within a few years. In these applications, a comparatively small amount of radiation extends the shelf life without causing the undesirable effects mentioned above.

The principle of cold sterilization is illustrated in Figure 41. Irradiated potatoes with improved storage quality are shown in Figure 42.

VOLTAGE PRODUCTION

There are several methods for direct production of electricity from the energy released in the decay of radioactive atoms. This energy is extremely minute compared with that from power reactors, but can be used for certain special applications requiring tiny amounts of power. The first of these methods utilizes a basic principle of physics. When a piece of dry plastic or hard rubber is stroked with a wool cloth, for example, the cloth sweeps off electrons from the surface of the dielectric material and leaves it with a positive charge. The wool cloth, of course, holds the negative charge.

Similarly, beta rays ejected from an insulated radioactive source leave it with a positive charge; this is the principle of the Moseley generator developed in 1913. The useful industrial application of this principle has been realized in the development of one type of atomic battery. This high-potential, low-current battery is illustrated in Figure 43.

Another battery takes advantage of the ion multiplication principle to produce electricity from radioisotopes. The electricity is generated by the high-energy beta particles emitted from Strontium 90. These high-energy electrons are used to bombard a pea-sized silicon P-N junction, the merging of two specialized types of silicon. The P-N junction, in turn, releases about 200,000 slow-moving electrons for each high-speed electron striking it. About one-millionth of a volt is produced, strong enough to cause an audible signal in a telephone receiver. The battery is about the size of a thimble and has a life expectancy of more than 20 years.

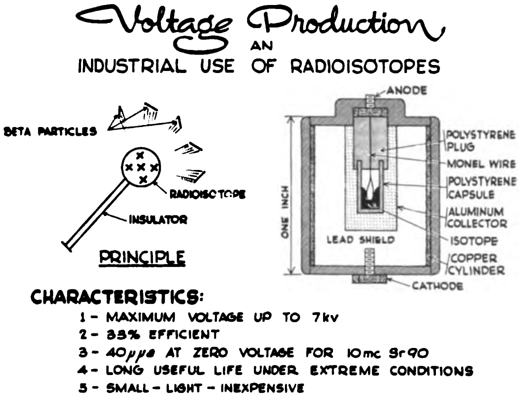


FIGURE 43.

Another very recent development has resulted in an atomic battery which uses a series of thermocouples to convert the heat from the decay of a radioisotope into electricity. The battery in its present form contains several curies of Polonium 210 sealed in a small capsule. The polonium is in contact with the hot junction of 40 thermocouples while the cold junction is located outside the container. The temperature difference of about 450° F. thus produced between the hot and cold junctions causes a current to flow through the device. This first model was found to be 0.2 percent efficient in transforming the energy from atomic decay into electricity.

A fourth type of atomic battery utilizes a radioactive source to ionize the filling gas between two electrodes of dissimilar metallic properties. Still another utilizes a radioisotope-activated luminescent source to energize a photoelectric cell, thus producing a small electric current.

TRACING ATOMS

Tracing atoms is perhaps the most important industrial use of radioisotopes. A few examples of the many ways in which the tracer principle is being used should illustrate its importance.

Wear Studies

Prior to World War II cyclotron-produced Phosphorus 32, added to the metal mix, was used to study the wear of piston rings. Today, conventional piston rings are made radioactive by subjecting them to neutron bombardment in reactors.

In such a bombardment, only one atom of iron in approximately one billion is converted from stable Iron 58 to radioactive Iron 59. The radioactive ring is fitted to the piston, using proper shielding and monitoring techniques. The engine is assembled, the lubricating oil is added, and the motor is started. Radioactive iron atoms are worn off the ring along with others and are easily detected in the oil. The sensitivity of the radioisotope method is so high that the wear of the ring can be detected in the first few minutes of running time.

The first such experiments were made primarily to determine engine wear as a function of the type of lubricating oil used, and have led to the production of oils that stand up better under severe operating conditions. It should be noted that it is not necessary to dismantle the engine to make the measurements. Both the rate and total wear can be measured readily. One company conducting such a study has indicated it was able to find out in 4 years for $35,000 what would have required 60 years and cost $1 million by older methods. Figure 44 illustrates this application of tracing atoms as an industrial use of radioisotopes.

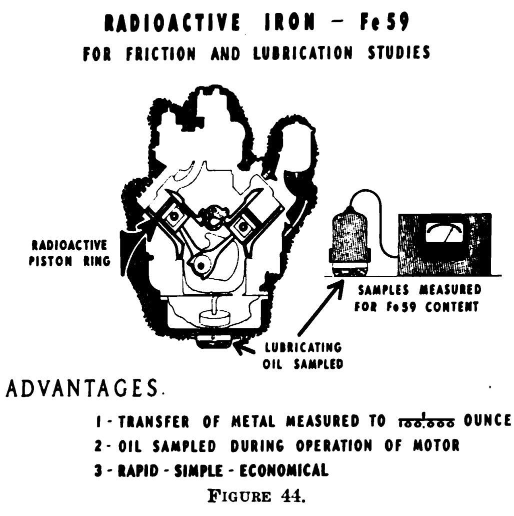


FIGURE 44.

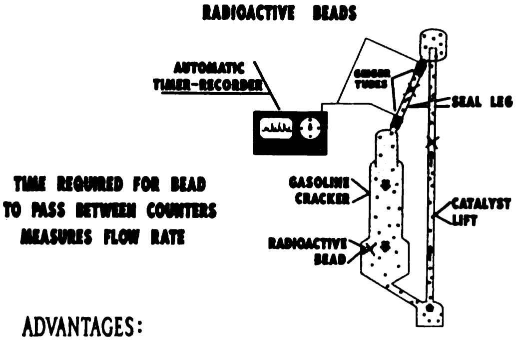
Tracing Catalyst Circulation

One of the simplest and most practical examples of the use of radiation to trace material is the determination of catalyst circulation in a catalytic cracking refinery. The catalyst, in the form of small porous beads, passes slowly down through the cracker, then to a furnace where the accumulated carbon is burned off, and finally back to the top of the cracker. The efficiency of this continuous operation is very dependent upon the rate of catalyst circulation, but it is extremely difficult to measure and thus to control this rate. Until recently it was determined by measuring temperature surges at various points in the cracker, even though this method required 2 man-days and did not give dependable results.

The isotopes technique now used for measuring the rate of catalyst circulation depends on impregnating a half-dozen or so of the few billion beads with radioactive zirconium, and noting the time required for a radiactive bead to pass between two rings of counters fastened at each end of a pipe between the gas lift and cracker. By knowing the weight of the catalyst in the pipe between the two points and the time interval between the two peak radiation readings, the operator can quickly calculate the catalyst circulation rate in tons per hour.

In its first application, this one simple test procedure eliminated the necessity for a $100,000 shutdown of a refinery. Today, this radioisotope procedure is used in a number of refineries for routine plant control. A chart in the control room keeps a continuous record of the flow and circulation of the catalyst. This application of tracing atoms is illustrated in Figure 45.

CONTROL OF CATALYST FLOW RATE
USING
RADIOACTIVE BEADS



ADVANTAGES:

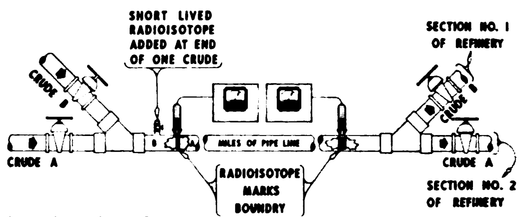
1—IMMEDIATE INDICATION OF IMPROPER OPERATION
2—NO INTERFERENCE WITH PRODUCTION
3—POSSIBLE AUTOMATIC ADJUSTMENT OF FLOW RATE

FIGURE 45.

Petroleum Product Flow

In another application in the petroleum industry, radioisotopes are used to mark the interface or boundary between two different petroleum products flowing through an overland pipeline. As illustrated in Figure 46 the location of the interface must be known in order to route different products to different take-off points and terminals along the line. The exactness with which the interface can be located determines the volume of product which must be considered as waste to assure that two unlike grades will not be mixed in the consumer product.

RADIOACTIVE ISOTOPES
FOR TRACING OIL FLOW IN PIPE LINES



ADVANTAGES:

1- RADIOACTIVE "MARKER" CAN BE TRACED OVER LONG DISTANCE
2- "MARKER" SPREADS TO ONLY SMALL OIL VOLUME
3- PERMITS SEPARATION OF CRUDES WITH MINIMUM OF LOSS
4- METHOD QUICK AND REQUIRES NO SAMPLING

FIGURE 46.

The radioisotope method is based on injecting into the line a small amount of radioactive material just at the interface as a different product is added. Geiger counters detect and record the passage of radioactivity in the interface at various points along the line. The isotope technique, which is now being used by a number of petroleum companies, has made it possible to reduce the volume of waste product at the final take-off point by one-third as compared to other methods for determining the location of the interface. The isotope technique has also proved helpful in determining the degree of mixing of various products as they pass through the pipeline.

Further, the technique has been used as a safety feature to start pumps operating automatically as the interface approaches, and thereby avoid the possibility of different products, say gasoline and stove oil, becoming mixed because of holdup in an idle pump.

Oil Well Acidizing

Still another tracer application of particular interest and economic significance to the petroleum industry is the use of radioisotopes in oil well acidizing. To increase the output of certain oil-bearing strata it is often necessary to increase the porosity of the strata with an acid treatment. In the past an undesirable feature of the process was the necessity for removing the tubing through which the acid was introduced before the control instruments could be used. This involved the hoisting and complete disjointing of as much as 10,000 feet of 2-inch pipe sections, a costly and hazardous operation.

The radioisotope technique which is less hazardous, less costly and much quicker, is illustrated in Figure 47. The technique is based on suspending in the pipe at the desired depth of acid treatment a radiation detector such as a geiger counter and adding a small quantity of radioactive material to the acid being used. As the acid containing the radioisotope passes down through the pipe, there is, of course, a response as it goes by the counter, but this response is not as great as when the labeled acid has filled the well to the height of the suspended detector.

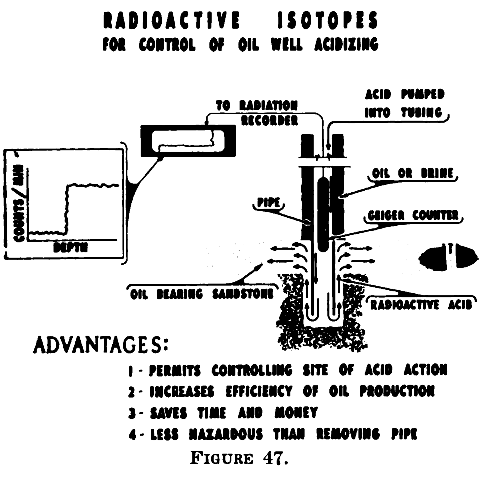


FIGURE 47.

A high radiation reading, therefore, means that the acid has reached the level at which the treatment should be made. At this time, pressure is applied to the system to force acid into the strata, while more acid is added to maintain the proper depth.

Leak Location

Somewhat related to flow indication and also to a test procedure is the use of radioisotope markers or tracers in leak detection. Perhaps the simplest application is the use of radiosodium or radioiodine in detecting leaks in water lines.

In this case a small quantity of the radioisotope is introduced into the line and the path of its radiation followed until it reaches the spot where the radiation reading drops off. In a number of instances these tests have made it possible to find and repair leaks in buildings with a minimum disruption of the structure. Furthermore, the test gives quick and reliable results where other techniques fail. This industrial use of radioisotopes is illustrated in Figure 48.

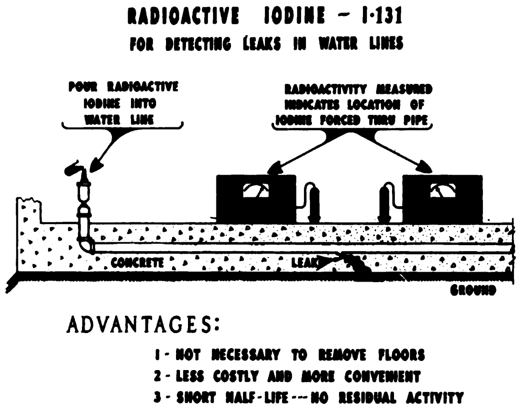


FIGURE 48.

Tracing Pirate Colors

Radioisotopes have been used as a "moving marker" to trace pirate colors. They provide a means of preventing what is called color soiling in multicolor textile printing operations. This occurs whenever one color is carried forward by the fabric from one printing roller to the

next, and may jeopardize the sale of many hundreds of yards of valuable fabric.

Any color is in danger of being contaminated by the preceding colors—especially by the immediately preceding one. It is not always possible to arrange the color sequence for printing such that the most sensitive colors are applied first. Frequent replacing of dye solutions is costly; hence, constant efforts must be made to prevent or reduce color contamination.

Many solutions to the problem were tried in the past but without practical success. However, radioisotopes now offer the ideal solution since the offending or so-called pirate color can be labeled with radioactivity and its gradual invasion of a sensitive color dye box carefully and continuously monitored

It is not necessary to synthesize a costly radioactive dye for this use. A few millicures of P–32 as soluble phosphate are added to the dye bath in question. Dip counters, as shown in Figure 49, are used to establish the initial specific activity of the pirate color and other dip counters continuously record the level of contamination in dye boxes further down the production line.

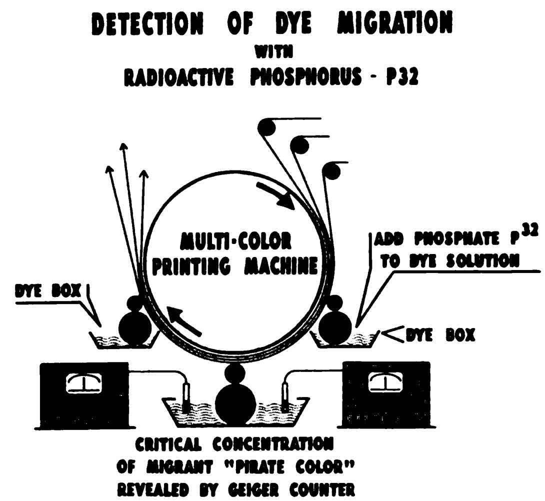


FIGURE 49.

Electron Printing

A recently developed application of radioisotopes in the field of fine arts may have industrial significance. As shown in Figure 50 a picture painted or printed with sufficiently long-lived radioactive ink can be reproduced as many times as desired simply by placing it in contact with photographic paper and then developing the image. An isotope emitting low-energy beta particles, such as Nickel 63, produces clear, sharp reproductions. On the other hand, a softened, diffused effect is obtained with the high-energy beta particles of Phosphorus 32, which can reach the photographic emulsion at an appreciable distance. Tones from light gray to black are obtained by repeated applications of the ink or with inks of different radioactive concentration.

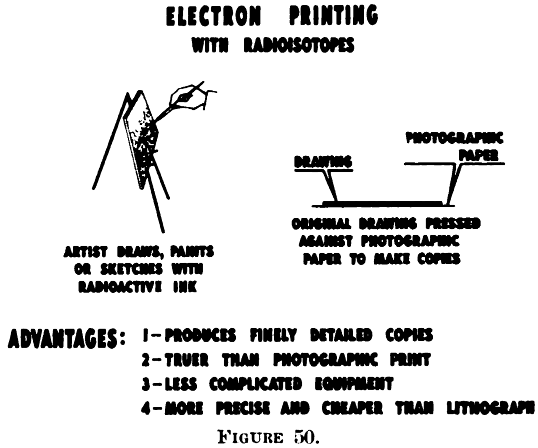


FIGURE 50.

Other Tracer Applications

The radioisotope technique has also been used for measuring the wear of gears, the contact wear of distributor points, and the wear of tire tread as a function of vehicle velocity. Similar techniques have been used for measuring the wear and life of machine cutting tools, for studying carbon brush wear during commutation of a direct-current motor, and for determining the wear of floor waxes.

The radioisotope technique is also adaptable to the study of wear caused by corrosion rather than by friction. For example, radiosulfur has been used to study the corrosion of gas-fired thermoelectric generators, radiosodium has been used to test the corrosion of refractories by molten glass, and radiocobalt has been used in determining the wear of fire brick in the lining of blast furnaces.

Space does not permit listing additional applications. However, the use of radioisotopes

in most tracing problems is a "natural" and awaits only the application of the technique to the problem at hand.

FUTURE INDUSTRIAL ASPECTS

There can be no doubt that radioisotopes hold many keys to present-day industrial problems. Many believe that radioactivity and the capabilities of the industrial atom will soon be as familiar to industrialists as electricity is today.

Recent developments in low-level radiation counting (counting just above the normal radiation level in nature) hold considerable promise for industrial use of radioisotopes. Using these very sensitive methods, tracer tests could be done during actual processing in an industrial plant and the products reaching the general public would contain such small amounts of radioactivity above the natural level that their handling and use would be completely safe.

Special electronic circuits that cancel out the natural radiation background permit easy measurement of harmless levels of radioactivity. Samples for measurement are usually placed directly into the counter gas or scintillation fluid.

Nature has herself shown how useful radioisotopes can be. For example, it is possible to distinguish recently living wood from wood long dead by means of the radiocarbon produced through the action of cosmic rays on nitrogen in the air. Organic chemicals derived from living materials can be distinguished from those derived from coal and oil. In a similar way, rainwater can be distinguished from groundwater by the radioactivity of naturally occurring radiohydrogen, or tritium.

Many tons of naturally occurring radiocarbon are distributed throughout the world in soil, atmosphere, water, etc. Growing things absorb and use the radioisotope along with stable carbon. At death, absorption stops. Using the decay of naturally occurring radioisotopes as timing devices, ages of things long dead can be accurately determined.

Low-level counting has not been explored to a great extent by industry. Techniques for measurements at these levels are well known, however, and need only industrial development.

Available Materials and Services

RADIOISOTOPES

Basic radioactive products available from Commission facilities:

1. Unprocessed irradiated materials
   - (a) Service irradiations of targets furnished by the applicant.
   - (b) Routinely irradiated batches or "units."
2. Chemically processed radioisotopes
   - (a) From target materials.
   - (b) From uranium (fission products).

   Processed radioisotopes are available from Commission distributors primarily in simple chemical forms.

Radioisotopes of elements of atomic number 1 to 84 inclusive are routinely available for all uses. Service irradiations of elements above atomic number 83 are not normally available but will be considered provided the target material will not affect the safety of the reactor or is not dangerous to handle.

The principal production unit in the United States is the air-cooled graphite reactor at Oak Ridge National Laboratory (ORNL). The Low Intensity Test Reactor at ORNL is used when its higher flux of 4×10^{13} neutrons per square centimeter per second is desirable.

A new facility which can separate and purify large quantities of fission products from used reactor fuels has been scheduled for construction at ORNL in 1956. The new plant will provide equipment for separation and purification of kilocurie quantities of important long-lived fission products and for fabricating them into large radiation sources. It will have the capacity for separation of approximately 200,000 curies per year of Cesium 137 as well as thousands of curies of Strontium 90 and other long lived fission products. At present only a few curies per month of such radioisotopes can be separated.

Irradiation services and certain special materials are available from Argonne National Laboratory, Brookhaven National Laboratory, Mound Laboratory, and National Reactor Testing Station. Brookhaven's program for development of production methods resulted in such additions to the list of available radioisotopes and services as Iodine 132, Fluorine 18 and special irradiations. Argonne has added the CP–5 reactor to the program, increasing the variety of special irradiations. Objects up to $15\frac{1}{2} \times 15\frac{1}{2} \times 60$ inches, for example, can be accommodated, and pneumatic "rabbits" can carry small samples through a flux of 2×10^{13} n/cm.^{2}/sec.

The materials Testing Reactor in Idaho, with a thermal neutron flux of 4×10^{14} n/cm.^{2}/sec., is now activating intense Cobalt 60 sources on a routine basis. The fast neutron flux of 2×10^{14} n/cm.^{2}/sec. in the Experimental Breeder Reactor can be made available for special irradiations.

Mound Laboratory in Ohio processes and sells Polonium 210 as a metal deposited on platinum foil or gauze, specially prepared alpha sources, and neutron sources.

In addition to the materials produced at these sites, certain materials with long life and high specific activity, such as Carbon 14, Iron 55 and Cobalt 60, are produced at Hanford Atomic Products Operation, Hanford, Wash., and distributed through the Radioisotope Sales Department at ORNL.

STABLE ISOTOPES

The stable isotopes distribution program has continued at a steadily increasing rate since its inception in 1947. For detailed data on distribution of stable isotopes refer to Appendix III.

Most of these isotopes are concentrated at Oak Ridge in the same type of electromagnetic separators which were used during World War II to separate fissionable Uranium 235 from Uranium 238. More than 200 concentrated stable isotopes of 50 elements are now routinely available.

SPECIAL SERVICES

Special Services from Commission Facilities: *Neutron activation analysis* involves irradiation of a sample in a nuclear reactor and subsequent identification of the radioisotopes produced. The analysis may be both qualitative and quantitative. Trace elements have been determined in biological materials, drugs, fertilizers, fine chemicals, foods, fuels, glass, insecticides, lubricants, metals, minerals, paints, petroleum products, plastics, soils, dusts, waters, toxicants and other materials.

Gamma service irradiations are available at most AEC reactor sites and also from a number of private laboratories. Gamma radiation in large enough doses can destroy bacteria in a material without raising its temperature significantly. Also, certain important chemical reactions or physical changes occur when the material is exposed to enough gamma radiation. These two uses of radiation are believed to hold many commercial potentialities. Large sources of Cobalt 60 and Tantalum 182 are used for most gamma irradiations, but highly active fuel elements from reactors are now coming into use.

Encapsulation of special radioisotope sources is provided at ORNL. All metalic Cobalt 60 to be used as radiation sources must be encapsulated prior to use. This safety precaution was found necessary since the surface of cobalt metal oxidizes. When handled, the oxide tends to flake off, and may present a hazardous contamination problem. ORNL encapsulates only large or special sources not available commercially.

Radioisotope waste disposal service is available at three AEC laboratories. ORNL will accept radiomaterials from users in all sections of the country. The Radiation Laboratory at Berkeley, Calif., will receive radiomaterials from users in the San Francisco Bay Area. ANL will assist in disposal of active waste resulting from materials irradiated at that Laboratory.

Materials and Services from Commercial Firms:

Much of the progress of the atomic energy program can be attributed to the close cooperation between private industry and government. In the field of isotope distribution and utilization, private industry has contributed extensively to the growth and development of the program. With the passage of the Atomic Energy Act of 1954, industry has new opportunities for greater industrial participation. There are numerous direct and indirect business opportunities found in the many uses of radioisotopes.

Labeled Compounds.—Many universities and research centers as well as industrial firms have contributed to developing new isotope-labeled compounds and improving existing production techniques. Nearly 1,000 labeled compounds are currently available from approximately 25 commercial suppliers.

Pharmaceuticals.—Bulk shipments of unrefined radioisotopes are purchased from ORNL, processed as pharmaceuticals, calibrated, and reshipped in small quantities to hundreds of individual users.

Teletherapy Units.—At the close of 1954, seven United States firms were collaborating with radiophysicists and therapists in developing radiation devices for specific medical purposes. The numerous variables, such as energy of radiation, specific activity of the radioisotope, source-skin distance, stationary versus rotation therapy, and protection of patient and personnel, have led to many possibilities and plans of use. The active development of teletherapy units incorporating large sources of radioisotopes shows much commercial promise.

Radiography exposure devices, or gamma-ray cameras, are now being manufactured and sold by several companies in the United States. More than 350 industrial firms in the United States are using radioisotopes for radiography. Many of these have purchased special exposure devices or fabricated their own in plant shops.

Radioactive thickness gages are currently available from six commercial firms and are being used by more than 300 companies to meet more exacting product specifications.

Medical applicators are now being manufactured by several commercial firms. Such devices include eye applicators for treating

ophthalmic lesions, beta-ray plaques for treating a variety of skin disorders, custom designed radiation needles for interstitial uses, colpostats for special medical use, a variety of radioisotopes sealed in plastic tubing for use as sutures, shielded syringes and a variety of other special devices.

Other materials and services account for a growing commercial business related to isotopes. These include the production of radiation measuring instruments, luminescent markers, static eliminators, and atomic batteries. Services include consultation, film meter service and radioisotope waste disposal.

LICENSING

The Atomic Energy Act of 1954 authorizes the Commission to issue general or specific licenses to applicants seeking to use byproduct material for research or development purposes, for medical therapy, industrial uses, agricultural uses, or such other useful applications as may be developed.

The act further provides that the Commission shall not permit the distribution of any byproduct material to any licensee, and shall recall or order the recall of any distributed material from any licensee, who is not equipped to observe or who fails to observe such safety standards to protect health as may be established by the Commission or who uses such material in violation of law or regulation of the Commission or in a manner other than as disclosed in the application therefor or approved by the Commission.

Regulations governing the manufacture, production, transfer, acquisition, ownership, possession, importation, or export of byproduct material have been published by the Commission under Title 10, Part 30, of the Code of Federal Regulations.

Exempt Quantities

Small quantities of certain beta- and gamma-emitting radioisotopes may be obtained and used without filing an application or receiving a license from the AEC. A detailed list of exempt items and quantities is published in the regulations.

Export and Imports

A program for the international distribution of radioisotopes was begun in 1947; stable isotopes were added to the program in July 1954. Isotopes and reactor-irradiated materials subject to USAEC regulations may be imported from other countries. Detailed data on the international distribution of isotopes appears in Appendix III.

RADIOLOGICAL SAFETY

To date, distribution of AEC-supplied isotopes has been accomplished by means of an authorization (or licensing) procedure. In the case of radioactive isotopes this procedure is designed to make the materials available under conditions which will assure their safe use. The Commission, through the Isotopes Division, provides the services of experts trained in radiological safety. Field visits are made to assist radioisotope users who have radiation protection problems. Consultation on specific isotope applications is not provided by the Commission. The latter type of service is available from a number of commercial firms and private consultants.

Recommendations of the National Committee on Radiation Protection are used as basic guides in development of safe practices in the use of radioisotopes and in the formulation of AEC standards for the protection of health. A list of National Bureau of Standards handbooks containing these recommendations appears in Appendix I.

Technical Services and Training Opportunities

The Commission has an extensive program for developing wider use of isotopes. Some of the important services are to:

1. Provide information on isotopic materials, procurement policies, and procedures.
2. Provide information on radiological safety in the storage, use, and disposal of radioisotopes.
3. Assist in developing and presenting radioisotope techniques training courses and in the production of training films and other visual aids.
4. Provide references on isotope uses.
5. Encourage industrial and commercial participation.

Training Films

The AEC gave extensive technical assistance to the Army Signal Corps in the preparation and production of a series of training films entitled "The Radioisotope." The series consists of individual films designed to offer instruction in the characteristics and measurement of radioisotopes, the techniques involved in their use, their safe handling, the biological effects of radiation, and finally, the ways in which radioisotopes have been used in medicine, industry, agriculture, and general sciences. They are intended for an audience of high professional, technical and educational level.

The films that have been completed are: (1) Fundamentals of Radioactivity, (2) Properties of Radiation, (3) Practical Procedures of Measurement, (4) Methodology, (5) Principles of Radiological Safety, (6) Practice of Radiological Safety, (12) Agricultural Research, and (13) General Sciences. Films in the series that have not yet been produced are: (7) Biological Effects of Radiation, (8) Medical Research, (9) Medical Diagnosis, (10) Medical Therapy, and (11) Industry and Engineering.

The films are available on loan to United States users from the AEC and from the various Army Headquarters' Central Film Libraries.

Slide Illustrations

An extensive series of line-drawing illustrations is available for use by educators, lecturers, and students. The subject matter includes isotope production, isotope characteristics, isotope distribution, and isotope applications in biology, medical research, diagnosis and therapy, agriculture, chemistry, physics, and industry. Copies of the illustrations in the form of 8 x 10-inch prints are available on loan from the Isotopes Division for reproduction purposes.

AEC-Sponsored Training

The Commission early realized the necessity for basic training in radioisotope uses and safe handling techniques. The application of these new tools can be expanded only as fast as people learn to use them. To assure health and safety, radiomaterials are distributed in quantity only to those who are trained to use them safely. The AEC has therefore actively encouraged the establishment of training opportunities in techniques and safety, both by its own laboratories and by private enterprise.

ORINS Training Courses.—The Oak Ridge Institute of Nuclear Studies was organized in 1946 by a group of universities, under contract with the AEC, to utilize the unique facilities of Oak Ridge in programs of research and training. In the summer of 1948, the Institute initiated a program of courses, of 4 weeks duration, in the basic techniques of radioisotope handling. These basic courses are still given. Scientific experts from nearby AEC groups frequently serve as lecturers. More than 1,400 graduates have returned to their own laboratories, hospitals, and firms with sufficient training to initiate a radioisotope program. The courses have served as a prototype for others established since by universities and private institutions.

ORINS also gives advanced courses in various specialized fields of radioisotope utilization. Leading authorities in the respective fields, both

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from within and outside the AEC, serve as lecturers and course leaders. About 600 participants have taken advantage of these special courses.

At the popular and semitechnical levels, the Institute maintains an Atomic Energy Museum which acquaints visitors with various aspects of atomic energy and radioisotope usage.

Radiological Physics Fellowships.—With the increasing usage of radioisotopes and the advent of nuclear reactors in universities and industry, there is an increasing need for institutional radiological safety officers. The AEC is helping to meet the need by providing fellowships in radiological physics to promising graduates of colleges and universities.

The fellowships provide for nine months in a university followed by three months of applied health physics training at one of the National Laboratories. The programs are carried out in three separate pairs of locations: at Vanderbilt University and Oak Ridge, at the University of Rochester and Brookhaven, and at the University of Washington and the Hanford Atomic Products Operation. More than 200 of these fellowships have been accepted and the graduates' specialized knowledge and training are being applied in AEC installations, universities, medical centers, industrial plants, and other institutions throughout the Nation.

On-the-Job Training.—Thousands of persons throughout the Atomic Energy Project are receiving training in the handling of radioactivity as an integral part of their work. Radiological Safety and Health Physics groups, in particular, are given extensive training in safety principles.

Many university and industrial people also are receiving valuable training in Commission laboratories. Their participation in development work, while on leave of absence, is mutually beneficial to the Commission and their home institutions. These researchers and engineers, as well as students in training centers such as the Oak Ridge School of Reactor Technology, receive broad knowledge in applications of atomic energy.

AEC Assistance.—In addition to its training opportunities, the Commission has encouraged this activity by others. The encouragement has taken many forms, such as suggestions and recommendations on programs and courses, review of proposed course content and training manuals, active participation by AEC personnel in programs and symposia, furnishing informational material, and loan of exhibits, lantern slide illustrations, and technical and nontechnical films. At the high school level, the American Museum of Atomic Energy at Oak Ridge instructs visiting student groups, aids in setting up "science fairs," maintains traveling exhibits, and sends teaching aids on request.

Medical Training

Training in medical techniques and safety with radioisotopes is proceeding at two general levels. First, orientation programs are offered by medical schools for undergraduate students, and by various medical groups for physicians who were already in practice when radioisotopes came into clinical use. At the second level, actual clinical training with patients enables the physician to employ radioisotopes in his own practice.

Programs of the first type have ranged from short lecture series to extended courses including lectures, detailed laboratory work, and clinical demonstrations. This type of orientation provides a background knowledge suitable for the medical man who wishes to understand the role of radioisotopes in his field.

At the second level referred to above, training is aimed directly at the use of radioisotopes in medical practice. The AEC's Advisory Committee on Isotope Distribution considers a definite period of clinical apprenticeship, with a physician or group actively using radioisotopes, essential for developing clinical judgment in the use of these materials.

Specialized opportunities for clinical training are made available in certain AEC research hospitals. One-year residencies, including stipend and maintenance, have been established at the cancer research hospital operated by the Medical Division of the Oak Ridge Institute of Nuclear Studies. These residencies offer an unusual opportunity to learn tracer and therapeutic techniques and are approved for basic credit in Internal Medicine. Similar residen-

cies have been established at the Argonne Cancer Research Hospital in Chicago.

The training of hospital technicians and pharmacists in the techniques of radioisotope handling and laboratory procedures relies, at present, on occasional on-the-job experience. The need for additional training opportunities in these specialties is becoming more acute and several technical training schools are starting to offer formal courses to fit these persons for new responsibilities with radioisotopes.

Industrial Training

Several industrial concerns have added radioisotope technique and radiological safety courses to their training schedule. These are usually geared to the company's needs. The amount of instruction necessary is governed by the complexity and extent of radioisotope usage, and ranges from a simple manufacturer's manual for use with a well-shielded, direct-reading thickness gage to a full-scale course in nuclear physics, instrumentation, and health physics for a large program involving industrial research and manufacturing.

Initiation of customer training courses by suppliers and manufacturers of radioactive devices has been another worthwhile step toward better radiological safety.

University Training

Most important from the long term standpoint has been the initiation of radioisotope courses in university extension programs and in graduate and undergraduate work. If the principles of radioisotope utilization are learned as part of the usual academic education there will be less need for intense, special training later.

Isotopes are used in over 200 universities and colleges. Many of these have initiated radioisotope laboratory courses or are presenting the fundamentals of the techniques where they apply in other course. Most of these universities are conducting research projects, often sponsored by the AEC, in which radioisotopes are involved and in which postgraduate students can obtain a familiarity with the principles of their use.

Secondary School Education

The introduction into the high school of laboratory experiments with radioactivity is, in some respects, the most noteworthy of recent developments in education. Concepts involved in counting and measuring radiations, in tracer studies, and in operating simple radiation equipment are readily adaptable to the high school level.

The use of radioisotopes in high school science demonstrations and in laboratory experiments by the students has been accelerated by the spreading awareness that small license-free quantities of radiomaterial can be purchased. When handled with reasonable care, the small amounts present little or no hazard. License-free quantities of radioisotopes are quite adequate for classroom experiments.

Other Training Opportunities

In recognition of increasing use of radiation and the associated health problems, the Public Health Service sponsors a radiological health training program in Cincinnati. The program includes 2-week courses designed for personnel of State and local health departments and a limited number of participants from other governmental agencies and industry.

An impressive amount of training in radioisotope handling and radiological safety is being sponsored by the Armed Forces, both because of the increased significance of such training in national defense and because of the widespread use of radioisotopes in the Service's medical research and clinical programs.

APPENDIX I

Special Sources of Information on Isotopes

Available From—

I. ISOTOPES DIVISION
U. S. Atomic Energy Commission
Oak Ridge, Tenn.

Forms and Instructions

AEC–313, "Application for Radioisotope Procurement" and Instructions.

AEC–375, "Radioisotope Order Blank" (for Federal Agencies).

AEC–465, "Certificate of Compliance with Federal Food, Drug, and Cosmetic Act."

AEC–100, "Stable Isotope Request."

Films and Illustrations

"Guide to the Training Film Series, 'The Radioisotope'."—Outlines purpose, scope and organization of series and contains a brief synopsis of each film. The individual films are on loan, without charge, at the Central Film Library of the Army Area in which the borrower resides and at the Isotopes Division, Oak Ridge, for isotope users.

"List of Slide Illustrations".—Listing variety of line drawing illustrations on various aspects and uses of isotopes. Available on loan as 8″ x 10″ prints for reproduction purposes.

II. SUPERINTENDENT OF DOCUMENTS
Government Printing Office
Washington 25, D. C.

"ISOTOPICS—Announcements of the Isotopes Division".—Quarterly bulletin of the Isotopes Division furnishing information on isotope procurement, allocation procedures, distribution policies, and methods for safe handling and disposal of radiomaterials. 35 cents per copy or $1 per volume (calendar year) by subscription.

"Isotopes . . . A Three-Year Summary of U S. Distribution," August 1949.—Summarizes isotope production and distribution and contains bibliography of over 1,850 references. 45 cents per copy.

"Isotopes . . . A Five-Year Summary of U. S. Distribution," August 1951.—Gives detailed account of all isotope investigations initiated from the beginning of the distribution program in August 1946 through June 30, 1951, indicating institution and department, principal investigator, isotope, purpose for which material was obtained, and status of investigation at date of publication or reference to published report, if any. Report also contains bibliography of 1,400 references (supplementing bibliography in 3-year summary). $1 per copy.

"Nuclear Science Abstracts".—Covers unclassified and declassified AEC research reports on Nuclear Science, and other material in this field which appears in technical and scientific journals and unpublished research reports of government agencies, universities, and industrial research establishments. 25 cents per copy or subscription at $6 a year domestic and $9 foreign.

TID–5098, "Use of Isotopes in Plant and Animal Research".—19 papers from Conference at Kansas State College, June 12, 1952. $1.25.

"The Contribution of Atomic Energy to Agriculture".—Hearings before the Subcommittee on Research and Development of the Joint Committee on Atomic Energy, Congress of the United States, March 31 and April 1, 1954. 25 cents.

"The Contribution of Atomic Energy to Medicine".—Hearings before the Subcommittee on Research and Development of the Joint Committee on Atomic Energy, Congress of the United States, June 2, 3, and 4, 1954. 55 cents.

National Bureau of Standards Handbooks

Handbook 42, "Safe Handling of Radioactive Isotopes." 15 cents.

Handbook 48, "Control and Removal of Radioactive Contamination in Laboratories." 15 cents.

Handbook 49, "Recommendations for Waste Disposal of Phosphorus 32 and Iodine 131 for Medical Users." 10 cents.

Handbook 51, "Radiological Monitoring Methods and Instruments." 15 cents.

Handbook 52, "Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water." 20 cents.

Handbook 53, "Recommendations for the Disposal of Carbon 14 Wastes." 15 cents.

Handbook 54, "Protection Against Radiations From Radium, Cobalt 60, and Cesium 137." 25 cents.

Handbook 56, "Safe Handling of Cadavers Containing Radioactive Isotopes." 15 cents.

Handbook 57, "Photographic Dosimetry of X- and Gamma Rays." 15 cents.

Handbook 58, "Radioactive-Waste Disposal in the Ocean." 20 cents.

Handbook 59, "Permissible Dose From External Sources of Ionizing Radiation." 30 cents.

Semiannual Reports of the AEC to Congress

Fourth Semiannual Report, "Recent Scientific and Technical Developments in the Atomic Energy Pro-

gram of the United States," July 1948. 35 cents (largely on isotopes program).

Sixth Semiannual Report, "Atomic Energy in the Life Sciences," July 1949. 45 cents.

Eighth Semiannual Report, "Control of Radiation Hazards in the Atomic Energy Program," July 1950. 50 cents.

Eleventh Semiannual Report, "Some Applications of Atomic Energy in Plant Science," January 1952. 50 cents.

Thirteenth Semiannual Report, "Assuring Public Safety in Continental Weapons Test," January 1953. 50 cents.

Fourteenth Semiannual Report, "Major Activities in the Atomic Energy Programs," January–June 1953. 45 cents.

Fifteenth Semiannual Report, "Major Activities in the Atomic Energy Programs," July–December 1953. 45 cents.

Seventeenth Semiannual Report of the Atomic Energy Commission, July–December 1954. 45 cents.

III. OFFICE OF TECHNICAL SERVICES
Department of Commerce,
Washington 25, D. C.

"Price List of Research Reports for Sale."—Titles and prices of available unclassified and declassified AEC research reports. Free of charge upon request.

AECU-2226, "Design of Laboratories for Safe Use of Radioisotopes."—By Donald R. Ward. 35 cents.

AECU-2821, "Air Contamination and Respiratory Protection in Radioisotope Work."—By G. W. Morgan and C. R. Buchanan. 25 cents.

AECU-2875, "Equipment for Radioisotope Laboratories."—By Oscar M. Bizzell. 25 cents.

AECU-2967, "Radiation Safety in Industrial Radiography with Radioisotopes."—By P. M. Frazier, C. R. Buchanan, and G. W. Morgan. 25 cents.

ANL-5111, "Annotated Bibliography in Radiobiology."—Abstracts of 2,153 reports and journal articles on radiation effects, radioelement metabolism, and effects on growth, genetics, and cytology. $2.10.

TID-3046, "Utilization of Gross Fission Products."—Bibliography of unclassified report literature. 25 cents.

TID-3050, "A Bibliography of Selected AEC Reports of Interest to Industry."—Brief abstracts.

Part 1, Metallurgy and Ceramics. 35 cents.

Part 2, Chemistry and Chemical Engineering. 45 cents.

Part 3, Nuclear Technology. 35 cents.

Part 4, Electronics and Electrical Engineering. 35 cents.

Part 5, Mechanics and Mechanical Engineering. 25 cents.

Parts 6 & 7, Construction and Civil Engineering; Mining and Geology. 25 cents.

Parts 8 & 9, Industrial Management: Health and Safety. 25 cents.

TID-4550, "Availability of U. S. Atomic Energy Commission Research and Development Reports."—Description of ways reports and other publications are made available to the public. Free of charge upon request.

TID-5078, "Radioisotope Applications of Industrial Significance."—Extracts the industrial uses from the listing in "Isotopes . . . A Five-Year Summary of U. S. Distribution" above. 30 cents.

TID-5115, "The Role of Atomic Energy in Agricultural Research."—25 papers from symposium at Oak Ridge, August 25, 1952. $3.10.

IV. OAK RIDGE NATIONAL LABORATORY
Radioisotope Sales Department
Post Office Box P
Oak Ridge, Tennessee

"Catalog and Price List of Radioactive and Stable Isotopes."—Gives price, chemical form, purity, specific activity, etc., of radioisotopes; chemical form and degree of enrichment of stable isotopes on loan; special materials and services; ordering and shipping procedures.

V. BROOKHAVEN NATIONAL LABORATORY
Isotopes and Special Materials Group
Upton, Long Island, New York

"Catalog and Price List of Reactor Irradiation Services and Radioisotopes."—Gives prices, specifications applying to target conveyor, shipping information, and instructions for ordering.

VI. ARGONNE NATIONAL LABORATORY
Special Materials Department
Post Office Box 299
Lemont, Illinois

"Catalog and Price List of Irradiation Services."—Gives information on availability of the irradiation facilities of ANL's Research Reactor—CP-5, Experimental Breeder Reactor and 60-Inch Cyclotron, and ordering and shipping procedures.

VII. McGRAW-HILL BOOK COMPANY, INC.
330 W. 42nd Street
New York 36, New York

National Nuclear Energy Series.—Complete technical record of scientific work carried out in the nation's atomic energy program under the Manhattan Project and continuing with that of the AEC (see TID-4550 above for titles and prices).

VIII. D. VAN NOSTRAND COMPANY, INC.
250 4th Avenue
New York 3, New York

"Sourcebook on Atomic Energy."—By Samuel Glasstone.—Description of theory, history, development, and uses of atomic energy and radioisotopes. $2.90.

IX. STANFORD RESEARCH INSTITUTE
Project 361
Stanford, California

"Industrial Uses of Radioactive Fission Products."—A report to the USAEC. $1.50.

APPENDIX II

Chronological Outline of Development of Isotopes Distribution Program

1. First public announcement of reactor-produced radioisotopes available under the distribution program appeared in the June 14, 1946 issue of *Science* (served as 1st Radioisotopes Catalog).
2. First reactor-produced radioisotope shipment from Oak Ridge, August 2, 1946.
3. Jurisdiction of program turned over to civilian Atomic Energy Commission, January 1, 1947.
4. Initiation of service irradiations, that is, a service whereby the radioisotope user may submit his own sample for irradiation or neutron bombardment in the nuclear reactor, March 1, 1947.
5. Initiation of program making available the concentrated stable isotopes of Boron 10 (complex), deuterium and deuterium oxide (heavy water), June 1947.
6. First compound labeled with radiocarbon (methyl alcohol) available from the Commission, July 1947.
7. Initiation of a program for international distribution of radioisotopes, September 3, 1947.
8. Formation of an Advisory Committee on Isotope Distribution (to replace interim policy committee set up under the Manhattan Project), January 1, 1948.
9. Initiation of a program for distribution on a loan basis of more than 100 varieties of electromagnetically concentrated isotopes of about 30 elements, January 21, 1948.
10. Publication of regulations by the Interstate Commerce Commission for shipment of radioisotopes by common carrier (rail and truck), January 25, 1948.
11. Opening of first Commission-sponsored training course in radiosotope techniques by Oak Ridge Institute of Nuclear Studies, June 1948.
12. Distribution of tritium (radioactive hydrogen) and stable Helium 3, September 1948.
13. Completion of a nation-wide intercomparison of Iodine 131 radiation analyses conducted by the National Bureau of Standards and Atomic Energy Commission.
14. Availability of stable elemental Boron 10 announced March 28, 1949.
15. Initiation of a program for cyclotron production and distribution of certain long-lived radioisotopes not producible in the nuclear reactor, June 1949.
16. Enactment of regulations by the Civil Aeronautics Board for shipment of radioisotopes by commercial aircraft, July 20, 1949.
17. Completion of new large-scale radioisotope processing facilities at Oak Ridge National Laboratory, March 15, 1950.
18. Announcement of program for returning radioactive wastes to Commission facilities for disposal, October 1950.
19. Initiation of cooperative visitation with state health departments to radioisotope users, December 1950.
20. Announcement that Brookhaven National Laboratory will provide reactor irradiation services and radioisotopes, January 1951.
21. Publication of first issue of the quarterly bulletin, "*Isotopics*—Announcements of the Isotopes Division," April 1951.
22. Expansion of international distribution of radioisotopes to include all reactor-produced radioisotopes (except tritium and Polonium 210) and to authorize the export of these materials for use in scientific research, medical research, industrial research, medical therapy and industrial applications, July 16, 1951.
23. First radioisotope (Iodine 131) accepted by Federal Food and Drug Administration as effective new drug, November 23, 1951; Phosphorus 32 accepted June 30, 1952; and Colloidal Gold 198 accepted October 1, 1954.
24. First film of thirteen-part radioisotope training film series, "The Radioisotope," made available for distribution, January 1952.
25. Announcement of availability of neutron activation analysis service at Oak Ridge National Laboratory, April 1952.
26. Publication of AEC-financed supplement to the Journal of the American Chemical Society on labeled-compound synthesis, May 1952.
27. Announcement of availability of facilities for irradiation of large items at Brookhaven National Laboratory, January 1953.
28. Publication in the Federal Register of criteria governing the authorization of AEC supplied radioisotopes for research and development, for human use, and for use under a general authorization. Use of license-exempt quantities of radioisotopes in humans expressly prohibited, December 15, 1953.
29. Publication by USAEC of list of 492 isotope-labeled compounds available from 13 commercial suppliers, the National Bureau of Standards, and Oak Ridge National Laboratory, January 1954.
30. Announcement of standard reactor units of radioisotopes, July 27, 1954.

31. Revision of Federal Radioisotopes Distribution Regulations to cover radioisotopes produced in any publicly or privately owned nuclear reactors located within the United States, its territories, or possessions, July 24, 1954.
32. Stable isotopes made available for export, July 1954.
33. Issuance of Argonne National Laboratory booklet, entitled "Irradiation Services" containing detailed information on services available at ANL's Research Reactor CP–5, Experimental Breeder Reactor, and its 60-inch cyclotron, September 1954.
34. Approval of Kilocurie Fission Product Separation Plant to be located at Oak Ridge National Laboratory, October 1954.
35. Announcement of Gamma Irradiation Facilities at National Reactor Testing Station to provide gamma-ray fields of the order of 10 million roentgens per hour, October 1954.

APPENDIX III

Statistics on Isotope Distribution

TABLE—"TOTAL ACTIVITY (Curies) AND SHIPMENTS OF PRINCIPAL ISOTOPES."
TABLE—"GROWTH IN ACTIVITY (Curies) AND SHIPMENTS."
TABLE—"TYPES OF INSTITUTIONS USING ISOTOPES IN THE UNITED STATES."
TABLE—"SHIPMENTS OF ISOTOPES TO COUNTRIES OUTSIDE THE UNITED STATES."
GRAPH—"GROWTH IN CURIES SHIPPED."
MAP—"RADIOISOTOPE USERS BY STATES."
MAP—"INDUSTRIAL FIRMS USING RADIOISOTOPES."

TOTAL ACTIVITY (Curies) AND SHIPMENTS OF PRINCIPAL ISOTOPES [1]

Isotope	Aug. 2, 1946–Dec. 31, 1953		Jan. 1, 1954–Dec. 31, 1954		Total to Dec. 31, 1954	
	Activity (Curies)	Shipments	Activity (Curies)	Shipments	Activity (Curies)	Shipments
Radioactive Isotope:						
Iodine 131	2, 026	18, 713	557	5, 023	2, 583	23, 736
Phosphorus 32	607	12, 059	153	2, 405	760	14, 464
Carbon 14	29	1, 649	5	269	34	1, 918
Sodium 24	23	1, 928	9	448	32	2, 376
Gold 198	688	1, 570	632	622	1, 320	2, 192
Hydrogen 3	346	149	168	94	514	243
Strontium 89, 90	138	646	119	130	257	776
Cobalt 60	20, 364	811	25, 493	134	45, 857	945
Cesium 137	52	411	327	104	379	515
Iridium 192	36	32	1, 200	99	1, 236	131
Polonium 210	312	56	819	57	1, 131	113
Other	379	13, 593	246	3, 200	625	16, 793
Total	25, 000	51, 617	29, 728	12, 585	54, 728	64, 202
Stable Isotopes:						
Deuterium Oxide	----------	682	----------	152	----------	834
Deuterium	----------	1, 052	----------	161	----------	1, 213
Boron 10, 11	----------	106	----------	64	----------	170
Helium 3	----------	25	----------	10	----------	35
Oxygen 18	----------	339	----------	48	----------	387
Electromagnetically Concentrated	----------	1, 957	----------	326	----------	2, 283
Argon 38	----------	4	----------	1	----------	5
Total	----------	4, 165	----------	762	----------	4, 927

[1] Distributed from Oak Ridge National Laboratory to all isotope users.

GROWTH IN ACTIVITY (Curies) AND SHIPMENTS [1]

Year	Curies Per Year	Shipments Per Year	Total Curies	Total Shipments	Year	Curies Per Year	Shipments Per Year	Total Curies	Total Shipments
1946	8	281	8	281	1951	4, 523	9, 475	6, 155	28, 899
1947	65	1, 897	73	2, 178	1952	11, 244	10, 691	17, 399	39, 590
1948	134	3, 618	207	5, 796	1953	[2] 7, 601	12, 027	25, 000	51, 617
1949	386	5, 633	593	11, 429	1954	[3] 29, 728	12, 585	54, 728	64, 202
1950	1, 039	7, 995	1, 632	19, 424					

[1] Distribution from Oak Ridge National Laboratory to all users.
[2] Decrease due to 20% charge for isotopes for cancer.
[3] Increase due to teletherapy units.

TYPES OF INSTITUTIONS USING ISOTOPES IN THE UNITED STATES

(Showing Number Added Each Year)

Year	Isotope	Medical Insts.	Colleges and Universities	Industrial Firms	Federal and State Labs	Foundations and Institutes	Other	Total
1946	Radioactive	38	22	18	4	4		86
	Stable	2	2	1				5
1947	Radioactive	48	26	17	5	7		103
	Stable	15	39	19	5	3		81
1948	Radioactive	31	21	21	8	5		86
	Stable	9	16	15	2	2		44
1949	Radioactive	27	20	47	15	3		112
	Stable	11	12	9	3	2		37
1950	Radioactive	62	34	103	17	10	1	227
	Stable	9	14	14	5	1	1	44
1951	Radioactive	101	31	165	68	5	2	372
	Stable	6	14	16	6	1		43
1952	Radioactive	138	24	212	40	9	2	425
	Stable	5	13	16	1	1		35
1953	Radioactive	206	20	210	44	4	10	494
	Stable	5	17	22	5	2	2	53
1954	Radioactive	219	14	227	36	6	9	511
	Stable	10	18	16	6	2		52
Total	Radioactive	870	212	1, 020	237	53	24	2, 416
	Stable	72	145	127	33	14	3	394

SHIPMENTS OF ISOTOPES TO COUNTRIES OUTSIDE THE UNITED STATES

Country	Radioisotope Total Sept. 3, 1947 to Dec. 31, 1954	Stable [1] Total July 1, 1954 to Dec. 31, 1954	Country	Radioisotope Total Sept. 3, 1947 to Dec. 31, 1954	Stable [1] Total July 1, 1954 to Dec. 31, 1954
Argentina	124		Colombia	8	
Australia	107		Costa Rica [2]		
Austria	1		Cuba	235	
Belgian Congo	2		Denmark	223	1
Belgium	145	2	Dominican Republic	1	
Bermuda	16	1	Egypt	2	
Bolivia [2]			El Salvador [2]		
Brazil	259		England	145	1
British West Africa	1		Finland	14	
Canada	674	6	France	111	8
Chile	99		Germany	24	

See footnotes at end of table

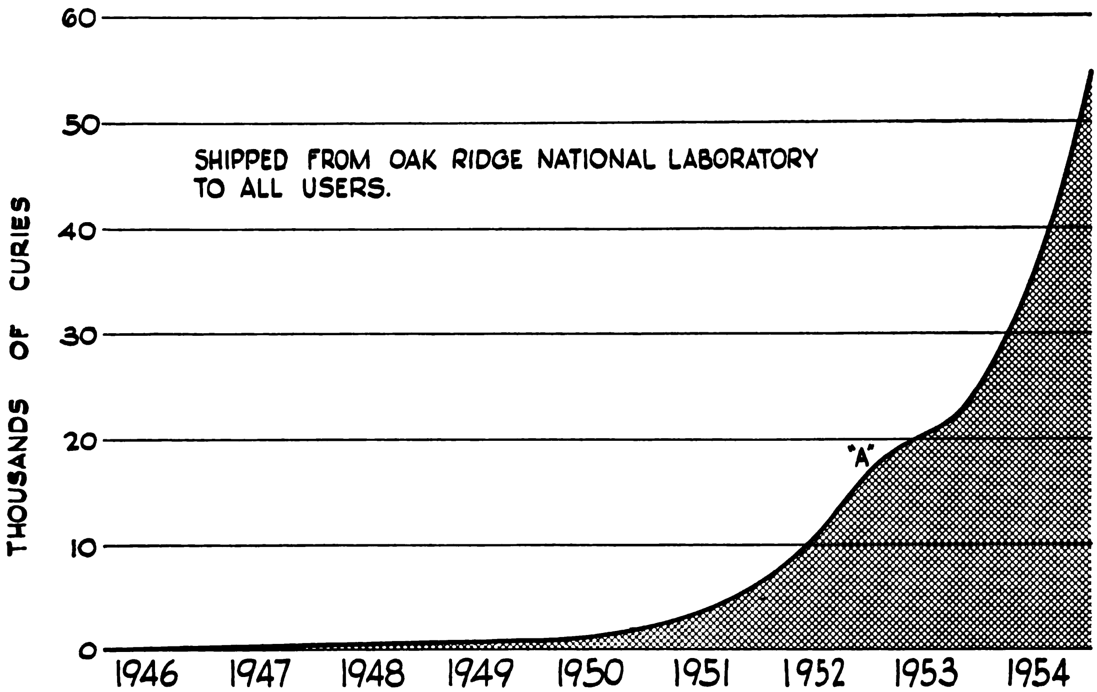
SHIPMENTS OF ISOTOPES TO COUNTRIES OUTSIDE THE UNITED STATES—Continued

Country	Radioisotope total Sept. 3, 1947 to Dec. 31, 1954	Stable[1] total July 1, 1954 to Dec. 31, 1954
Gold Coast	1	
Greece	1	
Guatemala	12	
Honduras [2]		
Iceland	5	
India	22	
Indonesia	3	
Ireland		
Israel	6	
Italy	34	1
Japan	330	
Lebanon	6	
Mexico	96	
Netherlands	57	
New Zealand	12	
Norway	43	
Pakistan	7	
Paraguay [2]		
Peru	20	
Philippines	2	
Portugal	5	
Spain	9	
Sweden	192	
Switzerland	63	1
Syria [2]		
Thailand [2]		
Trieste	3	
Turkey	5	
Union of South Africa	29	1
Uruguay	10	
Yugoslavia	1	
Venezuela	8	
Total	3, 173	21

[1] Stable isotopes became available for export July 1, 1954.

[2] Authorized to receive isotopes; no shipments made.

GROWTH IN CURIES SHIPPED
(CUMULATIVE TOTAL)

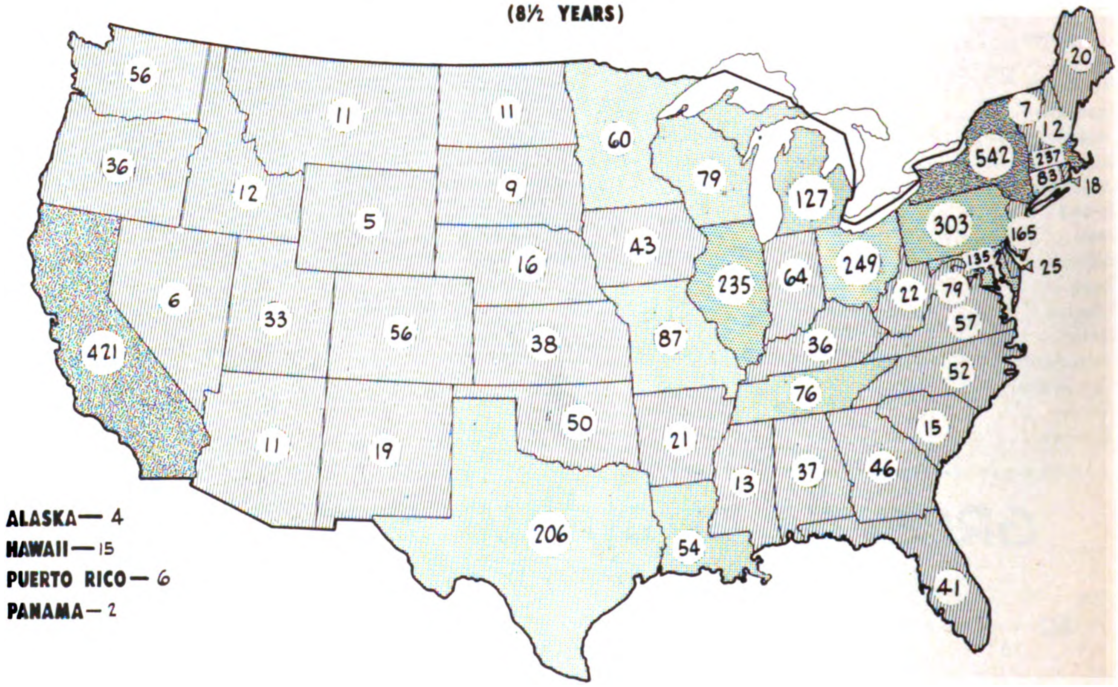


- DEFLECTION AT "A" DUE TO 20% CHARGE FOR CANCER ISOTOPES
- TOTAL CURIES - 54,728

RADIOISOTOPE USERS* BY STATES

AUGUST 2, 1946 — DECEMBER 31, 1954

(8½ YEARS)



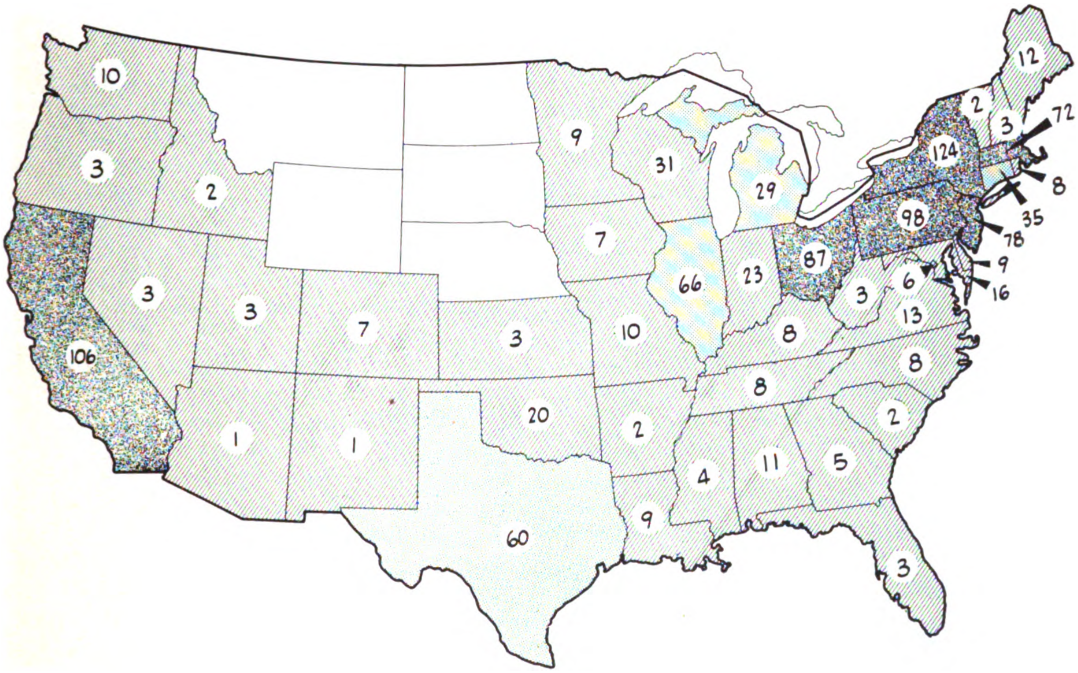
TOTAL NUMBER OF USERS — 4063

* APPLICANT (INSTITUTION, DEPARTMENT OR INDIVIDUAL)

INDUSTRIAL FIRMS USING RADIOISOTOPES

AUGUST 2, 1946 — DECEMBER 31, 1954

8½ YEARS



TOTAL 1020

APPENDIX IV

Extent of Chief Medical Uses of Radioisotopes

Isotope	Use		No. of Institutions Receiving AEC Licenses 1953	1954
I-131	Diagnosis	Thyroid function (diagnosis only)	80	80
		Blood volume and circulation	111	151
		Brain tumor	95	104
		Liver tumor	15	33
		Cardiac output	6	13
	Treatment	Hyperthyroidism	291	431
		Cancer	242	295
		Heart disorders	124	230
P-32	Diagnosis	Blood volume and circulation	37	50
		Tumor detection	39	49
	Treatment	Polycythemia and leukemia	269	389
		Skin cancer	4	10
		Other cancer	87	104
		Intracavitary	38	51
Au-198	Treatment	Intracavitary (including bladder)	131	209
		Prostate	32	45
		Other interstitial injection	43	39
		Intravenous	24	33
		Implants	3	7
Cr-51	Diagnosis	Blood volume	43	90
		Blood cell life	17	64
		Cardiac output	1	3
			1946-53	1946-54
Co-60	Treatment	Applicators (intracavitary and topical)	37	60
		Implants	18	36
		Teletherapy	28	46
Cs-137	Treatment	Teletherapy	[1] 8	[1] 8
Sr-90	Treatment	Applicators (ophthalmic and topical)	179	232
			1953	1954
Other isotopes	Diagnosis (other than above) Treatment (other than above) Studies in humans		131	156
	Diagnosis (including any above) Treatment (including any above) Studies in humans		[2] 15	[2] 17

[1] Three are for same machines as Co-60.
[2] Special general authorizations, with use unspecified.

NOTE.—Figures for the 2 years should not be added since licensees in 1953 usually appear also in 1954. Figures within a column should not be added since an institution usually is licensed for more than one use.

APPENDIX V

Bibliography

MORE than 7,000 references appear in the following bibliography. These are categorized into 30 fields of work with radioactive and stable isotopes supplied through the United States Atomic Energy Commission. Reference is made only to material which has been published during the 3½ years ending February 1955 or, more specifically, since publication of "Isotopes—A Five-Year Summary of U. S. Distribution."

The bibliography is restricted to open-literature references. Unclassified and declassified reports written by investigators working in Commission laboratories, but not published in the open literature, have not been included. These items are available as project reports at AEC depository libraries. Selected ones are on sale at the Office of Technical Services, Department of Commerce, Washington 25, D. C.

The bibliography is intended as a guide to persons interested in the technical aspects of isotope utilization. Being primarily concerned with isotopes as tools of research, it complements *Nuclear Science Abstracts* which can provide only limited coverage in this area. NSA is a semimonthly journal, published by the AEC, which covers reports and open literature on nuclear science.

The Isotopes Division staff has for the past few years scanned several hundred journals per month and maintained a card file on isotope uses. Each article is reviewed in sufficient detail to place it in an appropriate category. Although the card file is by no means complete, it served as a beginning for this bibliography.

In order to make the bibliography more complete, isotope users were requested to send lists of their publications. Because of the large number of references submitted, it was impossible to find and examine all the articles themselves. Instead, the title of each article was considered and an effort made to place it in an appropriate category. For this reason, a reference not appearing in the best category for the work actually reported may perhaps be found in a closely allied category.

Some references sent in had to be omitted. In certain cases the reference was not applicable to this coverage; in others the reference did not provide sufficient information to permit finding the article. Unfortunately several lists of references, particularly those from other countries, were received too late to be included.

The bibliography has been appended with an author index and a key to abbreviations used. The abbreviations are those used in the "List of Periodicals Abstracted by Chemical Abstracts."

Reference titles are listed alphabetically, except for additions at the end, within the following categories of isotope use:

Categories of Isotope Uses

References in this bibliography are broken down into the following categories

A Diagnostic Medicine.
B Therapeutic Medicine.
C Clinical Research.
D Human Physiology.
E General Medical Research.
F Immunology.
G Metabolite Physiology in Animals.
H Non-Metabolite Physiology in Animals.
I Injurious Agent Physiology in Animals.
J General Animal Physiology.
K Animal Husbandry.
L Bacteriology.
M Fertilizer Uptake by Plants.
N Plant Physiology.
O Photosynthesis.
P Radiation Effects on Living Organisms.
Q Biochemistry.
R Biosynthesis of Labeled Compounds.
S Chemical Synthesis of Labeled Compounds.
T General Chemistry.
U Reaction Mechanisms and Kinetics.
V Radiochemistry.
W Radiation Detection.
X Radiation Physics.
Y Nuclear Properties of Isotopes.
Z General Physics.
AA General Topics.
BB Isotope Techniques.
CC Applied Industrial Use.
DD Entomology.

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APPENDIX VI

Abbreviations Used in This Bibliography

Abstracts Fourth Intern. Cancer Research Cong. Abstracts of the Fourth International Cancer Research Congress.
Acta Physiol. Scand. Acta Physiologica Scandinavica.
Am. Foundryman. American Foundryman.
Am. Heart J. American Heart Journal.
Am. J. Botany. American Journal of Botany.
Am. J. Clin. Path. American Journal of Clinical Pathology.
Am. J. Hyg. American Journal of Hygiene.
Am. J. Med. American Journal of Medicine.
Am. J. Med. Sci. American Journal of the Medical Sciences.
Am. J. Obstet. Gynecol. American Journal of Obstetrics and Gynecology.
Am. J. Ophthalmol. American Journal of Ophthalmology.
Am. J. Path. American Journal of Pathology.
Am. J. Physiol. American Journal of Physiology.
Am. J. Psychiat. American Journal of Psychiatry.
Am. J. Roentgenol. Radium Therapy. American Journal of Roentgenology and Radium Therapy.
Am. J. Surg. American Journal of Surgery.
Am. Soc. Testing Materials, Proc. American Society for Testing Materials, Proceedings.
Anal. Chem. Analytical Chemistry.
Anat. Record. Anatomical Record.
Anesthesia & Analgesia. Current Researches in Anesthesia & Analgesia.
Anesthesiology. Anesthesiology.
Ann. Internal Med. Annals of Internal Medicine.
Ann. Rev. Plant Physiol. Annual Review of Plant Physiology.
Ann. Surg. Annals of Surgery.
Ann. Western Med. Surg. Annals of Western Medicine and Surgery.
Arch. Biochem. Archives of Biochemistry.
Arch. Ind. Hyg. Occupational Med. Archives of Industrial Hygiene and Occupational Medicine.
Arch. Internal Med. Archives of Internal Medicine.
Arch. Phys. Med. Archives of Physical Medicine.
Arch. Surg. Archives of Surgery.
Arkiv Kemi. Arkiv for Kemi.
ASTM Bull. American Society for Testing Materials, Bulletin.
Bell Lab. Record. Bell Laboratories Record.
Biochim. et Biophys. Acta. Biochimica et Biophysica Acta.
Biochem. J. Biochemical Journal.
Biol. Bull. Biological Bulletin.
Blood. Blood (Journal of Hematology).
Botan. Gaz. Botanical Gazette.
Botan. Rev. Botanical Review.
Bull. Am. Soc. Hosp. Pharm. Bulletin of the American Society of Hospital Pharmacists.
Bull. Johns Hopkins Hosp. Bulletin of the Johns Hopkins Hospital.
Bull. N. Y. Acad. Med. Bulletin of the New York Academy of Medicine.
Bull. soc. chim. biol. Bulletin de la societe de chimie biologique.
Bull. Torrey Botan. Club. Bulletin of the Torrey Botanical Club.
Calif. Citrograph. California Citrograph.
Cancer. Cancer.
Cancer Research. Cancer Research.
Can. J. Research. Canadian Journal of Research.
Can. Mining Met. Bull. Canadian Mining and Metallurgical Bulletin.
Cereal Chem. Cereal Chemistry.
Chem. Revs. Chemical Reviews.
Chicago Med. Soc. Bull. Chicago Medical Society Bulletin.
Circulation. Circulation.
Clin. Proc. Jewish Hosp. Clinical Proceedings of Jewish Hospital.
Cold Spring Harbor Symposia Quant. Biol. Cold Spring Harbor Symposia on Quantitative Biology.
Colo. Agric. Expt. Sta. Tech. Bull. Colorado Agricultural Experiment Station Technical Bulletin.
Conf. Liver Injury. Trans. 7th Meeting. Conference on Liver Injury. Transactions of Seventh Meeting.
Current Therapy. Current Therapy.
Dairy Science. Dairy Science.
Ecology. Ecology.
Elec. Eng. Electrical Engineering.
Elec. World. Electrical World.
Endocrinology. Endocrinology.
Euclides (Madrid). Euclides (Madrid).
Experientia. Experientia.
Exptl. Cell Research. Experimental Cell Research.
Farm Research. Farm Research.
Federation Proc. Federation Proceedings.
Gastroenterology. Gastroenterology.
Gen. Elec. Rev. General Electric Review.
Genetics. Genetics.
Glass Ind. Glass Industry.
Harper Hosp. Bull. Harper Hospital Bulletin.
Ind. Eng. Chem. Industrial and Engineering Chemistry.
India Rubber World India Rubber World.
Ind. Med. Surg. Industrial Medicine and Surgery.
Iron Steel Engr. Iron and Steel Engineer.
J. Am. Ceram. Soc. Journal of the American Ceramic Society.
J. Am. Chem. Soc. Journal of the American Chemical Society.

J. Am. Dental Assoc. Journal of the American Dental Association.
J. Am. Med. Assoc. Journal of the American Medical Association.
J. Oil Chemists' Soc. Journal of the American Oil Chemists' Society.
J. Am. Pharm. Assoc., Sci. Ed. Journal of the American Pharmaceutical Association, Scientific Edition.
J. Am. Vet. Med. Assoc. Journal of the American Veterinary Medical Association.
J. Animal Sci. Journal of Animal Science.
J. Applied Phys. Journal of Applied Physics.
J. Applied Physiol. Journal of Applied Physiology.
J. Bact. Journal of Bacteriology.
J. Biol. Chem. Journal of Biological Chemistry.
J. Cellular Comp. Physiol. Journal of Cellular and Comparative Physiology.
J. Chem. Education. Journal of Chemical Education.
J. Chem. Phys. Journal of Chemical Physics.
J. Clin. Endocrinol. Journal of Clinical Endocrinology.
J. Clin. Invest. Journal of Clinical Investigation.
J. Dental Research. Journal of Dental Research.
J. Econ. Entomol. Journal of Economic Entomology.
J. Electrochem. Soc. Journal of the Electrochemical Society.
J. Elisha Mitchell Sci. Soc. Journal of the Elisha Mitchell Scientific Society.
J. Exptl. Botany. Journal of Experimental Botany.
J. Exptl. Med. Journal of Experimental Medicine.
J. Exptl. Zool. Journal of Experimental Zoology.
J. Franklin Inst. Journal of the Franklin Institute.
J. Gen. Physiol. Journal of General Physiology.
J. Immunol. Journal of Immunology.
J. Infectious Diseases. Journal of Infectious Diseases.
J. Intern. Coll. Surgeons. Journal of the International College of Surgeons.
J. Lab. Clin. Med. Journal of Laboratory and Clinical Medicine.
J. Med. Assoc. State Alabama. Journal of the Medical Association of the State of Alabama.
J. Metals. (N. Y.) Journal of Metals (N. Y.).
J. Natl. Cancer Inst. Journal of the National Cancer Institute.
J. Nutrition. Journal of Nutrition.
J. Omaha Mid-West Clin. Soc. Journal of the Omaha Mid-West Clinical Society.
J. Optical Soc. Am. Journal of the Optical Society of America.
J. Org. Chem. Journal of Organic Chemistry.
J. Pharmacol. Exptl. Therap. Journal of Pharmacology and Experimental Therapeutics.
J. Phys. & Colloid Chem. Journal of Physical & Colloid Chemistry.
J. Polymer Sci. Journal of Polymer Science.
J. Research Natl. Bur. Standards. Journal of Research of the National Bureau of Standards.
J. S. Carolina Med. Assoc. Journal of the South Carolina Medical Association.
J. suisse pharm. Journal suisse de pharmacie.
J. Tenn. Acad. Sci. Journal of the Tennessee Academy of Science.
J. Urol. Journal of Urology.
Mech. Eng. Mechanical Engineering.
Med. Clinics N. Amer. Medical Clinics of North America.
Metal Finishing. Metal Finishing.
Mining Eng. Mining Engineering.
Modern Hosp. Modern Hospital.
Nature. Nature.
New Engl. J. Med. New England Journal of Mecicine.
New Orleans Med. Surg. J. New Orleans Medical and Surgical Journal.
Nucleonics. Nucleonics.
N. Y. J. Dentistry. New York Journal of Dentistry.
Ohio J. Sci. Ohio Journal of Science.
Oil Gas J. Oil and Gas Journal.
Pediatrics. Pediatrics.
Petroleum Engr. Patroleum Engineer.
Phys. Rev. Physical Review.
Phys. Today. Physics Today.
Physiol. Plantarum. Physiologia Plantarum.
Physiol. Revs. Physiological Reviews.
Plant Physiol. Plant Physiology.
Postgrad. Med. Postgraduate Medicine.
Poultry Sci. Poultry Science.
Practitioner. Practitioner.
Proc. Am. Electroplaters' Soc. Proceedings of the Educational Sessions of the Annual Convention of the American Electroplaters' Society for Horticultural Science.
Proc. Am. Soc. Hort. Sci. Proceedings of the American Society for Horticultural Science.
Proc. Inst. Radio Engrs. Proceedings of the Institute of Radio Engineers.
Proc. Natl. Acad. Sci., U. S. Proceedings of the National Academy of Sciences of the United States of America.
Porc. Natl. Sci. India. Proceedings of the National Institute of Sciences of India.
Proc. Roy. Soc. (London). Proceedings of the Royal Society (London).
Proc. Soc. Exptl. Biol. Med. Proceedings of the Society for Experimental Biology and Medicine.
Quart. J. Studies Alc. Quarterly Journal of Studies on Alcohol.
Radiology. Radiology.
Recent Progr. in Hormone Research. Recent Progress in Hormone Research.
Research Proc. Laurentian. Proceedings of the Laurentian.
Hormone Conf. Hormone Conference.
Research Revs. Research Reviews.
Rec. trav. chim. Recueil des travaux chimiques des Pays-Bas.
Rev. Sci. Instr. Review of Scientific Instruments.
Revs. Modern Phys. Reviews of Modern Physics.
S. A. E. Quart. Trans. Society of Automotive Engineers, Quarterly Transactions.
Science. Science.
Science Illus. Science Illustrated.

Sci. Monthly. Science Monthly.
Soap Sanit. Chemicals. Soap and Sanitary Chemicals.
Soc. Sci. Fennica Commentationes. Societas Scientiarum Fennica.
Phys.-Math. Commentationes Physico-Mathematicae.
Soil Sci. Soil Science.
Soil Sci. Soc. Am. Proc. Soil Science Society of America, Proceedings.
Southern Med. J. Stain Technol. Southern Medical Journal Stain Technology.
Surgery. Surgery.
Surg. Gynecol. Obstet. Surgery, Gynecology and Obstetrics.
Tappi. Tappi (Technical association of the pulp and paper industry).
Texas Repts. Biol. Med. Texas Reports on Biology and Medicine.
Texas State J. Med. Texas State Journal of Medicine.
Trans. Am. Geophys. Union. Transactions of the American Geophysical Union.
Trans, Am. Goiter Assoc. Transactions of the American Goiter Association.
Trans. Assoc. Am. Physicians. Transactions of the Association of American Physicians.
Trans. N. Y. Acad. Sci. Transactions of the New York Academy of Sciences.
Univ. Mich. Med. Bull. University of Michigan Medical Bulletin.
Vortex. Vortex.
Western J. Surg. Obstet. Gynecol. Western Journal of Surgery, Obstetrics and Gynecology.
World Oil. World Oil.
Yale J. Biol. Med. Yale Journal of Biology and Medicine.

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